Contemporary Management of Advanced Renal Cell Carcinoma

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Abstract: Kidney cancer is the eighth most commonly diagnosed cancer in the United States, and nearly one-third of patients have locally advanced or metastatic disease at presentation. Historically, survival outcomes for patients with advanced disease have been poor. In recent years, several novel targeted agents have emerged for the management of advanced renal cell carcinoma that have changed treatment paradigms. At the same time, surgical therapy continues to have a critical role in the management of selected patients. Recent medical and surgical advances have improved the prognosis for patients with a diagnosis of advanced disease. This review provides an overview of the current treatment landscape for patients with advanced renal cell carcinoma.

Keywords
Cytoreductive nephrectomy, immunotherapy, renal cell carcinoma, targeted therapy

Introduction

Kidney cancer is the eighth most commonly diagnosed cancer in the United States, with an estimated incidence of 63,990 new cases in 2017.[1] Owing in part to advances in cross-sectional imaging and the increased incidental detection of renal masses, the incidence of kidney cancer has risen steadily over the last 4 decades. Although many of the incidentally detected renal masses are small and at an early stage, a significant portion of patients with renal cell carcinoma (RCC) have advanced disease at presentation. Nearly 16% of patients present with distant metastatic disease, and an additional 16% present with evidence of regional lymph node spread. Although the 5-year survival rate for all patients with RCC is greater than 70%, those with metastatic disease have a 5-year survival rate of less than 12%.[1] Thus, optimizing outcomes in patients with advanced RCC remains a high priority for urologic surgeons and medical oncologists alike.

Management of Metastatic RCC

Cytoreductive Nephrectomy

Nearly 16% of patients with RCC have evidence of distant metastatic disease at the time of presentation.[1] Surgical therapy remains an integral tool in the management of selected patients with metastatic RCC (mRCC). The oncologic rationale for

cytoreductive nephrectomy (CN) in the setting of mRCC was established in 2 landmark prospective trials published in 2001. Both EORTC-30947 (Radical Nephrectomy Plus Interferon-Alfa-Based Immunotherapy Compared With Interferon Alfa Alone in Metastatic Renal-Cell Carcinoma)[2] from the European Organisation for Research and Treatment of Cancer Genito-Urinary Cancers Group and SWOG 8949 (Nephrectomy Followed by Interferon Alfa-2b Compared With Interferon Alfa-2b Alone for Metastatic Renal-Cell Cancer)[3] from the Southwest Oncology Group randomly assigned patients with mRCC to either radical nephrectomy followed by interferon alfa (IFN-α) or IFN-α alone. In the SWOG cohort, a 3-month overall survival (OS) benefit was demonstrated in the CN group (11.1 vs 8.1 months), and in the smaller EORTC cohort, a 10-month OS benefit was observed in the CN group (17 vs 7 months). A subsequent combined analysis of the 2 samples revealed a 6-month OS benefit of CN in the pooled cohort of 331 patients (13.6 vs 7.8 months).[4] These studies were the first to demonstrate prospectively a survival advantage for CN followed by systemic therapy compared with systemic therapy alone.

Patient selection in these landmark trials was of great relevance. Both trials selected patients with good performance status, no prior treatment, and no serologic evidence of hepatic or renal dysfunction. The EORTC trial additionally excluded patients with brain metastases. In subgroup analyses of the larger SWOG trial, the OS benefit of CN was most pronounced in patients with a smaller volume of metastatic disease, better performance status, and lung-only metastases. Subgroup analyses of the trials effectively established the paradigm of patient selection for CN, and the fundamental selection criteria derived from the 2 studies are still found in the National Comprehensive Cancer Network (NCCN) guidelines more than 15 years later.[5]

Subsequent studies further explored the effect of patient selection on survival outcomes and have attempted to refine predictive tools in CN. Both Culp and colleagues and Leibovich and colleagues developed distinct scoring algorithms to predict survival among patients undergoing CN.[6,7] However, the best-recognized prognostic scoring system for patients with mRCC was reported in a study by Motzer and colleagues from Memorial Sloan Kettering Cancer Center (MSKCC).[8] In an analysis of 463 patients with advanced RCC, the authors identified the following as factors associated with decreased OS: low Karnofsky performance status score; abnormal level of serum lactate dehydrogenase, hemoglobin, or calcium; and interval of less than 12 months from diagnosis to the initiation of systemic therapy. Although the study was intended to evaluate the outcomes of interferon therapy in patients with mRCC and was not explicitly designed to predict outcomes after CN, these risk factors have been widely used in the CN setting. Mekhail and colleagues validated this model in a cohort of patients with mRCC at the Cleveland Clinic and also added prior radiotherapy and specific sites of metastasis as negative prognostic factors.[9] Heng and colleagues similarly validated the MSKCC prognostic model in a multicenter cohort of 645 patients with mRCC.[10] These studies all highlight the importance of patient selection in CN. Regardless of the specific prognostic criteria used, CN entails potential morbidity and should be used judiciously only in the patients most likely to derive clinical benefit.

Although CN has become a well-established treatment option for appropriately selected patients with mRCC, the only prospective randomized studies in support of CN were conducted in the setting of treatment with IFN-α, a cytokine-based therapy that has been largely replaced by targeted therapy. Thus, the argument can be made that the evidence supportive of CN does not apply in the current era and is not relevant to contemporary treatment strategies.

To address this question, several authors have undertaken retrospective analyses of CN in the setting of targeted therapy. Choueiri and colleagues reported results in 314 patients who received anti–vascular endothelial growth factor (VEGF) therapy with or without CN.[11] Although the patients who underwent CN had more favorable prognostic factors at baseline, CN was independently associated with better OS on multivariate analysis that adjusted for baseline risk factors. Subgroup analyses suggested limited benefit of CN in patients with a low performance status score or those deemed to be poor-risk, mirroring trends seen in studies of CN in the cytokine era. Heng and associates similarly performed a retrospective analysis of 1658 patients who had mRCC and were treated with targeted therapy with or without CN.[12] Again, although the patients treated with CN had a better baseline prognosis, CN was independently associated with a survival advantage on multivariate analysis. This benefit was attenuated in those with the worst baseline prognosis. A meta-analysis of 11 retrospective studies including more than 39,000 patients confirmed a significant survival advantage of CN compared with targeted therapy alone.[13] Thus, although prospective randomized data supporting CN in the targeted therapy era are lacking, retrospective series do suggest a survival advantage of CN in the modern era.

Despite the previously presented retrospective data supporting the continued use of CN, large administrative database studies suggest that this treatment strategy may be underutilized in real-world clinical practice. Tsao and colleagues used the Surveillance, Epidemiology, and End Results (SEER) registry to demonstrate that use of CN decreased from 2005 to 2008, as targeted therapies gained

prominence.[14] This decline in the use of CN persisted even after adjustment for age, race, and ethnicity. A more recent analysis of the National Cancer Database suggested that of patients who received targeted therapy between 2006 and 2013, only one-third also underwent CN.[15] Although these population-based studies suggest an underutilization of CN in the targeted therapy era, large databases may lack sufficient granularity to determine how many patients are truly eligible candidates for CN.

Although CN was of clear benefit in the cytokine era, the paucity of prospective evidence in the targeted therapy era may be limiting its widespread use. In an overwhelming majority of the retrospective studies of CN with targeted therapy, the patients who underwent CN had inherently better prognoses at baseline, so that significant bias may have been introduced. However, a randomized trial, CARMENA (Clinical Trial to Assess the Importance of Nephrectomy), is currently under way that is comparing CN plus sunitinib (Sutent, Pfizer) therapy vs sunitinib alone.[16] This trial will help us understand whether CN truly offers a significant survival benefit in the era of targeted therapy.

Unfortunately, given how rapidly the arena of systemic therapy in advanced RCC is evolving, the CARMENA trial may soon become less relevant. Novel immunotherapy agents may well have replaced sunitinib and other targeted therapies by the time results from this randomized controlled trial become widely disseminated. This development may lead to concerns about applicability, analogous to concerns surrounding the applicability of the original EORTC and SWOG trials in the current era.

Role of Metastasectomy

In addition to CN, several authors have proposed surgical resection of metastatic lesions. Early reports of metastasectomy in the setting of mRCC seemed to indicate that surgery was feasible in selected patients.[17] In light of the early results, metastasectomy gained acceptance for patients with solitary metastatic nodules as well as for those with disease in multiple sites. In 2011, Alt and colleagues described their experience of metastasectomy in 887 patients with mRCC.[18] The authors demonstrated that cancer-specific survival was 4.8 years in patients who received a complete metastasectomy vs 1.3 years in those without a complete resection. On multivariate analysis, the risk for death was higher in the patients who did not receive a complete resection of metastasis than in those who did (hazard ratio [HR], 2.9; 95% CI 2.2-3.9). These results are consistent with those of another study, by You et al.[19] In this study, the patients who received a complete metastasectomy had a median OS of 92.5 months, whereas those who received either an incomplete metastasectomy or no metastasectomy had median OS times of 29.6 and 23.5 months, respectively (P <.001). A similar survival advantage with complete metastasectomy has been demonstrated in multiple other studies, further supporting the use of surgery for mRCC in the targeted therapy era.[20-22]

Recently, 2 large systematic reviews investigated the use of metastasectomy in patients with mRCC. In a study by Zaid and colleagues, the risk for all-cause mortality was greater in patients with an incomplete resection than in those with a complete resection of their metastatic disease (HR, 2.37; P<.001).[23] Similarly, in a meta-analysis, Dabestani and colleagues found that OS and cancer-specific survival were better in patients who had a complete resection of disease than in those who had an incomplete resection or no resection.[24] In addition, the authors found that in patients with metastatic disease of the lung, liver, or pancreas, metastasectomy conferred a survival advantage compared with no metastasectomy. Although resection is an option, it is important to note that studies have shown that metastasectomy is associated with significant complications,[25] highlighting the importance of careful patient selection. However, the overall body of literature suggests that metastasectomy is associated with prolonged survival in selected patients who have mRCC that is amenable to resection. It should be noted that these studies were all retrospective and may have been susceptible to selection bias. Specifically, the patients selected for metastasectomy tended to have higher performance status scores, fewer metastatic lesions with an overall smaller burden of metastatic disease, and a more favorable time between primary surgery and metastasectomy. Thus, the patients who underwent metastasectomy may have comprised a cohort with a more favorable prognosis at baseline, so that it is difficult to extrapolate the results of these studies to all patients with mRCC. Certainly, prospective randomized studies would help to elucidate the true benefit of metastasectomy in RCC.

Emerging Therapeutics

The development of first-generation VEGF and mammalian target of rapamycin (mTOR) pathway inhibitors has nearly doubled the OS time for patients with advanced and metastatic RCC who receive the appropriate sequence of available therapies.[26] Next-generation VEGF pathway inhibitors and immunotherapy checkpoint inhibitors have emerged recently and are rapidly becoming standards of care, increasing OS and improving toxicity profiles vs standard therapy.[27,28] Phase 2 and phase 3 trials of new agents that are currently in use for RCC are summarized in the table.

As experience grew with first-generation VEGF inhibitors, the elucidation of mechanisms of resistance led to next-generation therapeutics. Cabozantinib

Table. Phase 2 and 3 Trials of Emerging Therapies Recommended in NCCN, ESMO and/or EAU Guidelines as First- or Second-Line Treatments in Advanced or Metastatic Clear Cell Renal Cell Carcinoma

Trial Name, Reference, Year (Phase)	Treatment Arms	Patient Population	Primary End-point(s)	Secondary End-point(s)	OS (95% CI)[a]	PFS (95% CI)[a]	Patients With AEs Grade >3, %
METEOR, Choueiri,[30] 2016 (3)	Cabozantinib vs everolimus	N=658 Second-line tx for advanced ccRCC	PFS	OS, ORR	Cabozantinib: 21.4 (18.7-NE) Everolimus: 16.5 (14.7-18.8)	Cabozantinib: 7.4 (5.6-9.1) Everolimus: 3.8 (3.7-5.4)	Cabozantinib: 39% Everolimus: 40%
Motzer,[36] 2015 (2)	Lenvatinib + everolimus vs lenvatinib alone or everolimus alone	N=153 Second-line tx for advanced RCC	PFS	OS, ORR, AEs	Combination: 25.5 Lenvatinib: 19.1 Everolimus: 15.4	Combination: 14.6 Lenvatinib: 7.4 Everolimus: 5.5	Combination: 71% Lenvatinib: 79% Everolimus: 50%
CheckMate 025, Motzer,[40] 2015 (3)	Nivolumab vs everolimus	N = 821 Second-line tx for advanced ccRCC	OS	ORR, PFS, OS by PD-L1 tumor expression, AEs	Nivolumab: 25.0 (21.8-NE) Everolimus: 19.6 (17.6-23.1)	Nivolumab: 4.6 (3.7-5.4) Everolimus: 4.4 (3.7-5.5)	Nivolumab: 19% Everolimus: 37%
CheckMate 214, Escudier,[44] 2017 (3)	Nivolumab + ipilimumab vs sunitinib	N=847 (N=1096 in ITT population) First-line tx for advanced ccRCC	OS, ORR, PFS	OS, ORR, PFS in ITT population	Combination: NR[b] (99.8% CI, 28.2-NR) Sunitinib: 26.0 (22-NR)	Combination: 11.6 (99.1% CI, 8.5-15.5) Sunitinib: 8.4 (7.0-10.8)	Combination: 46% Sunitinib: 63%

[a] Results are displayed in months with 95% CI unless otherwise specified.

[b] Results reported are for the primary endpoint group.

AE, adverse event; ccRCC, clear cell renal cell carcinoma; ESMO, European Society for Medical Oncology; EAU, European Association of Urology; ITT-intention-to-treat; NCCN, National Comprehensive Cancer Network; NE, not estimable; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; tx, treatment.

(Cabometyx, Exelixis) is an inhibitor of multiple tyrosine kinases (TKIs) that targets not only VEGF but also c-MET and ALK, which commonly play a role in resistance to VEGF inhibitors. The phase 3 METEOR trial (A Study of Cabozantinib vs Everolimus in Subjects With Metastatic Renal Cell Carcinoma) compared cabozantinib with everolimus (Afinitor, Novartis) as second-line therapy after progression on VEGF therapy. Progression-free survival (PFS) was longer in the cabozantinib group than in the everolimus group (7.4 vs 3.8 months).[29] The OS benefit was 21.4 months with cabozantinib vs 16.5 months with everolimus, so that cabozantinib was the first TKI monotherapy to demonstrate OS benefit.[30] The phase 2 CABOSUN trial (Cabozantinib-s-malate or Sunitinib Malate in Treating Patients With Previously Untreated Locally Advanced or Metastatic Kidney Cancer) compared cabozantinib vs sunitinib in the first-line treatment of RCC and found an improvement in PFS.[31,32] This finding suggests a potential upcoming role for cabozantinib in the first-line space in advanced RCC.

Success with both VEGF and mTOR inhibitors led to the exploration of combination therapy. Early efforts were limited by toxicity and less-than-synergistic outcomes.[33-35] More recently, a combination of lenvatinib (Lenvima, Eisai), a third-generation multiple TKI, and everolimus was shown to confer a PFS benefit compared with either agent alone in patients whose disease had progressed after VEGF therapy.[36] PFS was 14.6 months for combination therapy vs 5.5 months with single-agent everolimus and 7.4 months with single-agent lenvatinib.

The concept of immunotherapy for RCC dates to cytokine therapy for advanced RCC in the 1990s. However, the toxic effects of interleukin 2 and IFN-α

are greater than those of the newer agents, and they are rarely used in the modern era. Although interleukin 2 is the only agent to have demonstrated a durable complete response, unfavorable toxicity has limited its use to young, fit patients with low-volume metastases and primarily clear cell histology. The emergence of checkpoint inhibitors has revolutionized the treatment of many solid tumors, including RCC. Nivolumab (Opdivo, Bristol-Myers Squibb), a programmed death 1 monoclonal antibody, is the first checkpoint inhibitor approved for use in mRCC. The programmed death 1/programmed death ligand 1 (PD-1/PD-L1) pathway serves as an inhibitory signal for T-cell effector function, preventing deleterious autoimmunity under healthy conditions. Overexpression of PD-L1 in roughly 30% of RCC tumors allows malignant cells to "escape" targeting by the immune system through the interaction of PD-L1 with PD-1 on the T-cell surface. As a result, the activation of T-cell effector function initiated by the binding of tumor cell antigen to the T-cell receptor (TCR) is inhibited.[37] RCC expression of PD-L1 is a poor prognostic indicator and is correlated with higher rates of cancer-specific death and distant metastasis.[37-39]

CheckMate 025 (Study of Nivolumab vs. Everolimus in Pre-Treated Advanced or Metastatic Clear-cell Renal Cell Carcinoma) is a phase 3 trial that compared nivolumab with everolimus in patients with mRCC who had received prior treatment. OS was 25 months in the nivolumab group compared with 19.6 months in the everolimus group.[40] Nivolumab additionally has a favorable side effect profile; better quality of life was demonstrated in the nivolumab group vs the everolimus group.[41]

Whereas nivolumab is an anti–PD-1 antibody, atezolizumab (Tecentriq, Genentech) is an engineered anti–PD-L1 monoclonal antibody. Atezolizumab had a favorable toxicity profile in a phase 1 trial that included 70 patients with mRCC, with 17% of patients experiencing a grade 3 adverse event (AE) and no instances of grade 4 AEs.[42] The objective response rate (ORR) with atezolizumab was 15% for the entire cohort and 22% in patients with unfavorable histology (Fuhrman grade 4 and/or sarcomatoid features). Atezolizumab is currently being investigated in combination therapies in phase 1 and phase 2 trials.[27]

Cytotoxic T-cell lymphocyte–associated antigen 4 (CTLA-4) is another T-cell surface checkpoint receptor that serves to dampen the immune response. Ipilimumab (Yervoy, Bristol-Myers Squibb) is a CTLA-4 inhibitor that has been tested in a phase 2 trial of advanced RCC. Interestingly, the ORR was 30% in patients with autoimmune AEs compared with 0% in patients without autoimmune toxicity.[43] Although the performance of CTLA-4 pathway inhibitor monotherapy overall has not been impressive, these agents have shown promise in combination with PD-1/PD-L1 inhibitors. In the phase 3 CheckMate 214 trial (Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma), OS and ORR were better with combination nivolumab and ipilimumab than with sunitinib in treatment-naive patients who had advanced RCC.[44] OS for intermediate- and poor-risk patients was not reached for the combination arm and was 26.0 months in the sunitinib arm.

Given the steady influx of new data from recently completed and ongoing clinical trials, national oncology organizations have updated their guidelines for the treatment of advanced RCC. The NCCN, European Society for Medical Oncology (ESMO), and European Association of Urology (EAU) guidelines now recommend nivolumab and cabozantinib as preferred second-line options for advanced RCC.[5,26,32] The NCCN also includes lenvatinib in combination with everolimus as a valid option for second-line therapy. Significantly, the EAU recently updated its guidelines in response to the CheckMate 214 trial results, recommending ipilimumab in combination with nivolumab for first-line therapy in patients with intermediate- and poor-risk RCC, the primary role of VEGF inhibitors having been superseded.[45]

Despite the emergence of these novel therapies, the vast majority of patients eventually fail to respond to multiple treatment options. It is unclear which individuals will respond to the various therapies available. A further understanding of appropriate sequencing is paramount, and the identification of biomarkers that can predict response to individual treatments is needed to improve patient selection.

Management of Metastatic RCC With Non–Clear Cell Histology

Non–clear cell RCC (nccRCC) accounts for approximately 20% of all cases of mRCC.[46] Unlike clear cell RCC, nccRCC encompasses a group of tumors with heterogeneous histologic types; the most common is papillary RCC, followed by chromophobe RCC, collecting duct carcinoma, renal medullary carcinoma, and unclassified RCC.[47] Each of these classifications represents a distinct disease state with unique genetic and molecular features. Thus, it is not surprising that responses to therapies targeting clear cell RCC, for which the preponderance of research has been conducted, are poor in patients with nccRCC.[48]

The 2007 ARCC (Global Advanced Renal Cell Carcinoma) trial was the first to establish temsirolimus (Torisel, Pfizer), an mTOR inhibitor, as a viable treatment for nccRCC. In this phase 3 clinical trial, which investigated the use of temsirolimus, IFN-α, or combination therapy in 626 patients with poor-risk mRCC, temsirolimus demonstrated an OS advantage.[49] Subgroup analysis showed a greater benefit of temsirolimus

in patients with nccRCC than in those with clear cell RCC (tumor reduction rates of 68% and 59%, respectively), although the difference was not statistically significant.[50] Median OS in the temsirolimus groups was 11.6 months. On the basis of these data, temsirolimus has become the only treatment for nccRCC in poor-risk patients to receive an NCCN category 1 recommendation. It has an NCCN category 2A recommendation for nccRCC in all other risk groups.[5]

Another mTOR inhibitor, everolimus, has been investigated in metastatic nccRCC for the following reasons: (1) efficacy in clear cell RCC, (2) preliminary data suggesting favorable responses to other mTOR inhibitors in nccRCC, and (3) easy administration via the oral route. Koh and colleagues enrolled 43 patients with metastatic nccRCC in a single-arm phase 2 trial (23 patients with prior VEGF therapy) to receive everolimus.[51] PFS was 5.2 months, and 10% of the patients exhibited a partial response. The RAPTOR trial (RAD001 as Monotherapy in the Treatment of Advanced Papillary Renal Cell Tumors Program in Europe) was another single-arm phase 2 trial that enrolled 92 treatment-naive patients with papillary histology to receive everolimus.[52] PFS was 4.1 months, and 65% of the patients had stable disease after 6 months. Everolimus has received an NCCN category 2A recommendation for patients with metastatic nccRCC.[5]

VEGF inhibitors have become a mainstay of treatment for clear cell RCC and are another class of drugs that has been investigated for nccRCC. Sunitinib has shown modest efficacy in several single-arm trials. Molina and colleagues treated 23 patients who had metastatic nccRCC (35% papillary) with sunitinib.[53] Median PFS was 5.5 months, and 15 patients (65%) had stable disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Another group enrolled 31 patients (71% papillary) with nccRCC.[54] Partial responses occurred in 11 patients, and 17 had stable disease for a median duration of 12.7 months. PFS was 6.4 months. The largest trial to date of sunitinib for advanced nccRCC studied 57 patients (47% papillary) with nccRCC, including patients with more than 20% sarcomatoid histology.[46] A partial response occurred in 3 patients, and median PFS was 2.7 months. Median PFS for the 5 patients with chromophobe histology was 12.7 months. Sunitinib is an NCCN category 2A preferred option for metastatic nccRCC.[5] Sorafenib (Nexavar, Bayer HealthCare/Onyx) is another anti-VEGF therapy that has shown activity in clinical trials comparable with that of suntinib.[55,56] However, a retrospective review of patients with metastatic nccRCC who received first-line treatment with sunitinib or sorafenib found a significant PFS advantage for sunitinib (11.9 vs 5.1 months, respectively).[57]

To date, 3 large, multicenter, randomized phase 2 clinical trials have compared sunitinib with everolimus for the treatment of metastatic nccRCC. In the ESPN trial (Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma), sunitinib showed a slight advantage in median OS and PFS compared with everolimus (16.2 vs 14.9 months and 6.1 vs 4.1 months, respectively), although these results were not statistically significant.[58] This trial closed early after interim analysis of the 68 patients showed that statistically significant superiority could not be reached for everolimus. The ASPEN trial (A Randomized Phase II Trial of Everolimus Versus Sunitinib in Patients With Metastatic Non-Clear Cell Renal Cell Carcinoma) enrolled 108 patients with treatment-naive metastatic nccRCC.[59] In this study, PFS was significantly increased when sunitinib was compared with everolimus (8.3 vs 5.6 months). A significant difference in OS was not found. In the ESPN trial, 40% of the patients had papillary histology, compared with 66% in the ASPEN trial. The ESPN trial also included patients with sarcomatoid tumors (17.6%), which may explain the shorter PFS compared with the ASPEN trial. RECORD-3 (Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients With Metastatic Renal Cell Carcinoma) was a multicenter, randomized phase 2 trial comparing everolimus followed by sunitinib at progression with the standard sequence of sunitinib followed by everolimus in patients with mRCC.[60] Post hoc subgroup analysis of 66 patients with nccRCC revealed a PFS advantage for sunitinib followed by everolimus (7.2 vs 5.1 months, respectively). Taken together, these data suggest a slight advantage of sunitinib over everolimus for the treatment of metastatic nccRCC.

Recent studies in metastatic nccRCC have focused on pathway-specific treatments for nccRCC subtypes. For example, foretinib is an inhibitor of MET, a pathway implicated in type 1 papillary RCC. In a phase 2 trial, Choueiri and associates enrolled 74 patients with advanced papillary RCC to receive foretinib.[61] Median PFS was 9.3 months, and the rate of response to therapy was higher in patients with germline *MET* mutations. In a similar study, patients with advanced or metastatic papillary RCC were given savolitinib, another selective MET inhibitor.[62] Median PFS for patients with *MET*-driven disease was 6.2 months, compared with 1.4 months for patients with *MET*-independent disease. These data emphasize the fact that nccRCC comprises heterogeneous pathologic states, and future studies must target the distinct biological and molecular pathways for each subtype.

Management of Locally Advanced RCC

Neoadjuvant Therapy for Complex RCC

Surgical resection remains a key tool in the treatment of locally advanced and metastatic RCC. Many tumors,

however, are not amenable to surgical resection owing to a very large size, bulky adenopathy, or the involvement of adjacent organs and critical vascular structures. Moreover, patients with the requirement for nephron-sparing surgery may have large, locally advanced, or hilum-encasing tumors that prevent safe nephron-sparing surgery. New management strategies to facilitate the safe surgical resection of otherwise unresectable tumors and improve the feasibility of partial nephrectomy in patients with RCC and strong indications for nephron-sparing surgery are urgently needed. The relative success of targeted molecular therapy, compared with prior systemic modalities, has generated interest in using these agents in the neoadjuvant setting.

Preoperative treatment with TKIs appears to reduce tumor size modestly in locally advanced and metastatic RCC. Retrospective analyses of patients with unresectable primary tumors who were treated with sunitinib revealed an objective response in 42% to 80% of tumors, with a 10% to 27% mean reduction in tumor diameter. By RECIST criteria, 16% to 25% of patients had a partial response.[63-65] The effects were less substantial in subsequent phase 2 trials. In patients with locally advanced and metastatic disease, preoperative sorafenib and sunitinib shrank the diameter of 76% to 80% of primary tumors by a mean of 10% to 12%. By RECIST criteria, only 5% to 7% of these cases qualified as a partial response.[66,67] More striking results were seen in a prospective trial of preoperative axitinib (Inlyta, Pfizer) in patients who had locally advanced tumors without metastasis. An objective response was observed in all the tumors, and 46% met RECIST criteria for a partial response.[68] Taken together, these data suggest a significant, albeit small, reduction in primary tumor size with neoadjuvant therapy in advanced RCC.

Patients with pressing indications for renal preservation and large, complex, or hilum-encasing tumors may benefit from neoadjuvant targeted therapy. To explore this possibility, 5 urologists reviewed 22 tumors before and after treatment with neoadjuvant axitinib. Although interobserver variability was significant (κ=.61), the tumors were 22.8 times more likely to be deemed amenable to nephron-sparing surgery following neoadjuvant axitinib.[69] Supporting these findings, a phase 2 trial of neoadjuvant pazopanib (Votrient, Novartis) in patients with complex tumors and indications for nephron-sparing surgery found that 46% of patients for whom partial nephrectomy had been deemed unsafe were ultimately able to undergo nephron-sparing surgery. Interestingly, the authors noted an elevated risk for urine leak (20%) following partial nephrectomy.[70] These limited data suggest that targeted therapy may facilitate partial nephrectomy, although at the cost of increased surgical complications.

A growing body of data supports the preoperative use of TKIs to facilitate complex partial nephrectomies in patients with otherwise unresectable locally advanced tumors. The role of neoadjuvant immune therapy is unknown, but phase 2 trials of preoperative immune checkpoint inhibitors, including PD-1, PD-L1, and CTLA-4 inhibitors, are accruing patients. Additionally, the randomized controlled trial PROSPER RCC (Perioperative Nivolumab vs. Observation in Patients With Localized Kidney Cancer Undergoing Nephrectomy) is currently enrolling patients to compare neoadjuvant nivolumab plus surgery vs surgery alone in high-risk nonmetastatic RCC. Moving forward, randomized trials will continue to clarify the role of neoadjuvant agents in complex renal tumors.

Role of Lymph Node Dissection During Surgery

The role of lymphadenectomy in RCC remains controversial. The anatomic pathway for lymphatic drainage from the kidneys varies widely and is further complicated by alterations in lymph and vascular drainage when malignancy is present. A study by Johnsen and colleagues in 1997[71] examined more than 500 patients with RCC at the time of autopsy and found that lymph node involvement was confined to the paracaval or para-aortic region in only 0.9% of cases, raising concerns that the therapeutic window of lymphadenectomy for providing any clinical benefit may be prohibitively small.

Numerous studies have been conducted to clarify the role of lymphadenectomy in localized cT1-T2 RCC. The most comprehensive study to date is EORTC 30881 (Radical Nephrectomy with and without Lymph-Node Dissection),[72] a prospective randomized controlled trial spanning 2 decades that accrued more than 700 patients with clinically localized (cN0M0) disease and randomly assigned them to radical nephrectomy with or without node dissection.[72] The data demonstrated no differences in survival, PFS, or time to disease progression between the 2 groups. Although some have raised concerns about a low rate of pathologically positive nodes in this study, the clinical trial was designed to determine the oncologic utility of lymph node dissection in clinically node-negative localized kidney cancer. Thus, we interpret these results to imply that no oncologic benefit is derived from lymph node dissection during surgery for localized kidney tumors. The EAU guidelines advise against routine lymph node dissection in patients without clinically appreciable nodal disease.[45]

In stark contrast, the role of lymphadenectomy in patients with high-risk disease (cT3-T4, high Fuhrman grade, sarcomatoid features, tumor necrosis, or cN1) is less clear. A previous retrospective study by Pantuck and colleagues included patients with N1 and/or M1 disease

and identified a survival benefit for lymphadenectomy on univariate analyses.[73] Similarly, a review of the SEER database focusing on patients with M0 disease undergoing nephrectomy and lymphadenectomy identified a correlation between the number of nodes retrieved and disease-specific survival (irrespective of the number of positive nodes).[74] More contemporary studies, however, have called these findings into question. Subgroup analysis of the ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) trial[75] and retrospective data from Gershman and colleagues[76] have failed to identify any survival benefit in patients with high-risk M0 disease undergoing lymphadenectomy.

Taken together, the data on this controversial topic suggest that in patients with low-risk localized disease, the benefit of lymph node dissection is small. Lymphadenectomy, however, is indicated in patients with clinically node-positive disease and is often performed in well-selected patients with high-risk disease.

Conclusion

The management of locally advanced and metastatic RCC is rapidly evolving. The last decade has seen the development of numerous novel targeted therapeutic agents, many of which show promise to alter the treatment landscape for advanced RCC significantly. At the same time, surgery continues to have an integral role in selected patients, and its benefits have the potential to be maximized further as the utility of neoadjuvant and adjuvant targeted therapies becomes better understood. Ultimately, recent advances in the management of advanced RCC have the potential to improve long-term oncologic outcomes, reduce morbidity, and improve quality of life for our patients.

Disclosures

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