

# Perioperative Approaches to Kidney Cancer

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**Abstract:** This article provides an overview of the perioperative treatment strategies available for renal cancer. A review of the literature via PubMed, ClinicalTrials.gov, the American Urological Association, and the American Society of Clinical Oncology was used to evaluate the perioperative treatment modalities that best fit renal malignancies according to subtype and stage. For metastatic renal cell carcinoma, among other cancer types, the advent of novel targeted molecular therapies has completely changed the therapeutic landscape. Therapy directed against vascular endothelial growth factor receptor (VEGFR), mammalian target of rapamycin (mTOR), and programmed death 1 (PD-1) has demonstrated clinically robust effects in metastatic disease, leading to significantly enhanced control of the overall tumor burden. Today, systemic therapy is the primary option for advanced kidney cancer. The surgical approach is the mainstay of therapy for localized renal cancer, with systemic options considered only in high-risk patients. More than a decade's worth of clinical trial evaluation has consistently demonstrated a limited contribution of antiangiogenic therapy in localized renal cancer, and the role of multimodality therapy in the localized setting is still evolving. It remains unclear which patients are most likely to benefit from a perioperative approach in metastatic renal cancer. Optimization of timing, choice of presurgical and postsurgical treatment strategies, and choice of neoadjuvant and adjuvant systemic therapies are discussed, along with the designs of current and future clinical trials.

## Introduction

In the United States, renal cancer has an annual incidence of more than 70,000 (with a 60:40 male-to-female ratio) and a 20% to 25% mortality rate. Surgical resection of localized renal cell carcinoma (RCC) yields a 5-year survival rate of 93%, but disease recurs in 25% of these patients during follow-up.<sup>1</sup> Approximately 25% of patients who have RCC present with metastases, and only 12% of these patients are expected to live another 5 years.<sup>2</sup> Survival is expected to continue to improve with advances in systemic therapy.

## Keywords

Neoadjuvant treatment, perioperative treatment, renal cancer

The marked prevalence of RCC, coupled with its aggressive potential and ability to show up in any form, necessitates a well-rounded treatment strategy. Historically, the likelihood of cure or remission in advanced kidney cancer was negligible. Now, novel pharmacologic advancements in kidney cancer are offering substantial hope by producing long-term remissions. Contemporary systemic therapy has not only become the mainstay in treating patients with metastatic renal cancer, it is also helping to redefine the role of nephrectomy in this group of patients.

This article has been constructed to highlight the best systemic and surgical therapies to date for each stage of renal cancer. Efforts to identify areas of improvement in the preoperative, intraoperative, and postoperative settings may help streamline the therapeutic sequencing as the paradigm shifts from surgical resection alone to initial systemic therapy and later cytoreductive nephrectomy (CN).

### Role of Surgery in Localized RCC

The incidence of RCC continues to rise steadily, largely because of risk factors that include tobacco use, hypertension, obesity, and—most conspicuously—the increased use of imaging. Localized renal cancer now accounts for more than 60% to 70% of new RCC cases.<sup>1</sup> Renal masses that suggest cancer include enhancing solid renal lesions and Bosniak III and IV complex cystic lesions. The management options available for RCC include radical nephrectomy (RN), partial nephrectomy (PN), thermal ablation, cryoablation, and active surveillance. To date, surgery remains the most important and the lone curative approach in localized RCC.<sup>2</sup> The efficacy of adjuvant or neoadjuvant therapy has not been completely proven in these patients, and only one systemic therapy has US Food and Drug Administration (FDA) approval: sunitinib (Sutent, Pfizer), which has been approved as adjuvant therapy following nephrectomy for RCC.

The updated guidelines have shifted from a one-size-fits-all approach to individualized decision-making that factors in the patient's age, comorbidities, tumor characteristics, and renal function. Nephron-sparing options, particularly PN, should be considered in place of RN if they are feasible and do not compromise cancer control. Biopsies of renal masses, thermal ablation, and active surveillance play a role in appropriately selected patients.

### Partial vs Radical Nephrectomy

As previously discussed, the primary role of PN and RN is in localized RCC. PN is a nephron-sparing procedure that is designed to preserve kidney function. PN has been linked to increased surgical risk, whereas RN has been linked to an increased risk for chronic kidney disease. Several randomized

trials have demonstrated equal oncologic outcomes with PN and RN, and noninferiority of PN to RN in solitary masses smaller than 5 cm.<sup>2-7</sup> On the basis of these data, guidelines have recommended PN as the standard treatment for T1a tumors.<sup>8-10</sup> The guidelines are less favorable for PN in the context of T1b tumors and are relatively divided between the 2 surgical modalities.

The overall survival (OS) benefit of PN and RN in T1 RCC tumors was examined in a retrospective multicenter study. PN was found to be beneficial in male patients, especially in those 75 years of age or younger ( $P=.0005$ ). However, PN was not beneficial for female patients or for male patients older than 75 years. The OS for RN in females was the same as the OS for PN in males, regardless of age.<sup>11</sup> The indications for PN in female patients and in all patients older than 75 years should be convincing, particularly given the perioperative risks. No rationale is found for this gender difference, and the results of this study have not been reproduced in other databases. In patients with T1 or T2 disease who are not candidates for PN, RN may be used. The recommendations favor laparoscopic RN over open RN in these patients because laparoscopic RN is associated with less morbidity.<sup>12-16</sup>

### Cancer Staging

The staging system of the American Joint Committee on Cancer uses TNM (tumor node metastasis) categories to quantify the extent of spread and for clinical risk stratification.<sup>17</sup> T describes the size of a tumor in the tissue of origin and any spread into nearby tissue. N refers to the spread of cancer to local lymph nodes. M refers to metastasis, which is the spread of cancer to other regions of the body. The combination of the values for these 3 variables determine the stage of a cancer (Table 1).

In this system, symbols (numbers or letters) appear after each letter that provide more detail about the cancer. X indicates the inability to determine the size of a primary tumor (TX), whether it is present in regional lymph nodes (NX), or whether it has metastasized (MX). A 0 following T, N, or M means that no cancer is present or none has been found at the respective division of staging. The size or extent of a primary tumor is indicated by numbers ranging from 1 through 4, with a higher number indicating a larger size (eg, T4 means a tumor that is locally advanced in size and growing into neighboring tissue). Regional node involvement is indicated by the numbers 1 through 3, which refer to the number and location of lymph nodes that contain cancer. In essence, the higher the number after the N, the more lymph nodes that contain cancer. Distant metastasis is indicated by the number 1 following M. The lowercase letters a, b, and c are subdivisions indicating further detail about tumor size and extent (Table 1).

**Table 1.** TNM System for Cancer Staging

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T1-2	N1	M0
	T3	N0 or N1	M0
IV	T4	Any N	M0
	Any T	Any N	M1

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor $\leq 7$ cm in greatest dimension, limited to the kidney
T1a	Tumor $\leq 4$ cm in greatest dimension, limited to the kidney
T1b	Tumor $>4$ cm but $\leq 7$ cm in greatest dimension, limited to the kidney
T2	Tumor $>7$ cm in greatest dimension, limited to the kidney
T2a	Tumor $>7$ cm but $\leq 10$ cm in greatest dimension, limited to the kidney
T2b	Tumor $>10$ cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)

TNM, tumor node metastasis.

## Recurrence of RCC

Multiple prognostic factors, such as tumor stage, nuclear grade, overall performance status, and molecular markers have been studied to help predict RCC recurrence. The greatest risk for recurrence of RCC occurs within the first

5 years after nephrectomy.<sup>18</sup> Tumor stage plays an important role in the timing of recurrence. After nephrectomy, the recurrence rate of T1 tumors has been reported to be 7%, with a median time to recurrence of 38 months. The recurrence rate of T2 tumors is 26%, with a median time to recurrence of 32 months, and the recurrence rate of T3 tumors is 39%, with a median time to recurrence of 17 months.<sup>19</sup> Depending on the size and extent of local tumors before resection, the incidence of local recurrence may range from 1.8% to 27%; one study reflected the lower limit, with a 5-year incidence of 1.8% in a population undergoing nephrectomy for localized RCC.<sup>20</sup> PN has generally been advocated for localized RCC lesions that are less than 4 cm in diameter. Despite the fears of higher local recurrence rates following PN, local recurrence rates of 1.2% to 9% have been reported.<sup>21,22</sup>

## Ablative Therapy

The increased use of diagnostic imaging techniques, specifically abdominal ultrasonography and computed tomography, has led to an increase in the discovery of small, solid renal masses. These tumors typically are relatively slow-growing, detected at earlier stages, and localized to the kidney.<sup>23</sup> Although nephrectomy has been the gold standard treatment for localized tumors, a shift has occurred toward treating small, incidentally found renal neoplasms in a nephron-sparing manner; this practice has offered oncologic and functional outcomes that are equivalent to those achieved with RN among patients with renal tumors that are 4 cm or smaller.<sup>24</sup> Ablative techniques offer advantages over extirpative techniques: reduced perioperative morbidity, shorter hospital stays, faster recovery, and the ability to treat patients who are poor surgical candidates while preserving renal tissue.<sup>25</sup> Radiofrequency ablation (RFA) and cryoablation both appear to be safe and effective minimally invasive methods of treating small renal tumors. Long-term data are still needed to prove the efficacy and durability of both ablative technologies.

RFA is a heat-mediated method of tissue destruction. In recent years, RFA has become the most commonly used percutaneous ablative technique for RCC. Its use has been described in patients with small renal tumors who have poor renal reserve, those with multiple bilateral RCCs in von Hippel–Lindau disease or with other hereditary RCCs, and those who are poor candidates for surgery.<sup>26</sup> Contraindications include coagulopathies, acute infection, a recent myocardial event, and poor life expectancy. Large tumors ( $>4$  cm) and tumors in the hilum or the collecting system are predictive of RFA failure. Additionally, the most commonly adverse effects of percutaneous RFA are pain and paresthesia at the site of electrode insertion.<sup>27</sup>

In cryoablation, argon or nitrogen with a cryoprobe is used to freeze the target tissue laparoscopically or percutaneously. This creates a cryolesion, which then undergoes necrosis and eventually heals by secondary intention. The freezing causes direct intracellular damage, in addition to changes in the extracellular osmotic concentration that lead to cell membrane dysfunction.<sup>28</sup> Unlike RFA, cryoablation requires real-time monitoring of the ice ball to ensure that the tumor is completely frozen and to minimize injury to the surrounding healthy tissue. As with RFA, pain and paresthesia at the site of probe insertion have been the most commonly reported complications.

## Adjuvant Therapy

Radical surgical resection is curative for a large proportion of patients with stages I through III RCC. The 5-year survival rate is greater than 90% among patients with stage I RCC. However, the 5-year relapse rate is 30% to 40% among those with stage II or III RCC; the median time to relapse is 18 months, and the majority of relapses occur within 3 years after surgical resection.<sup>12</sup> Reduction in the risk for relapse through adjuvant therapy is thus a very important goal in intermediate- to high-risk early-stage RCC.

Adjuvant trials of cytokine-based immunotherapy (eg, interferon alfa [IFN- $\alpha$ ] and interleukin 2 [IL-2]) were undertaken in RCC because of the established efficacy of these agents in stage IV RCC, in which they were once considered standard therapy (Table 2). However, none of the adjuvant trials of these agents, either as lone therapy or in combination, demonstrated a statistically significant improvement in disease-free survival (DFS) or OS.<sup>29-32</sup>

A randomized study published in 2003 also showed that the combination of 5-fluorouracil, IFN- $\alpha$ , and IL-2 did not produce a survival benefit and caused significant toxicity, with 35% of patients not completing treatment.<sup>33</sup> Adjuvant cytokine treatment was not recommended. Owing to the benefits seen with targeted therapy for metastatic RCC, several randomized controlled trials were launched to investigate their significance in the adjuvant setting.

In the S-TRAC (Sunitinib Treatment Of Renal Adjuvant Cancer) trial, 615 patients with localized (T3, T4, or N1) clear cell RCC who were at high risk for recurrence were randomly assigned in a 1:1 ratio to sunitinib or placebo. Sunitinib was found to prolong DFS significantly vs placebo (6.8 years vs 5.6 years, respectively;  $P=.03$ ).<sup>34</sup> OS data are not yet mature, but sunitinib is approved by the FDA for consideration in this setting. Although this trial may instill hope regarding the use of adjuvant therapy in these selected patients, the results conflict with those of the earlier ASSURE/ECOG E2805 (Sunitinib Malate or Sorafenib Tosylate in Treating Patients With Kidney Cancer That Was Removed By Surgery) trial. This trial,

in which 1943 patients were randomly assigned in a 1:1:1 ratio to sunitinib, sorafenib (Nexavar, Bayer), or placebo, showed no difference in DFS (the primary endpoint) or OS.<sup>35</sup> The discrepant outcomes have been partially blamed on differences in baseline risk between the 2 trials, given that the inclusion criteria of S-TRAC had a higher-risk renal cancer threshold (grades 3 and 4, per modified UCLA Integrated Staging System criteria) than did the inclusion criteria of ASSURE (tumors of any grade). This would suggest an increased likelihood of micrometastatic disease in the S-TRAC population and, consequently, a population with a potentially greater gain from adjuvant therapy. Furthermore, a subgroup (~20%) of patients enrolled in ASSURE had non-clear cell histology, which may have attenuated the sunitinib effect, whereas no patients of this subgroup were enrolled in S-TRAC.<sup>36</sup>

Other adjuvant trials, of pazopanib (Votrient, Novartis) and axitinib (Inlyta, Pfizer), also did not show a clear benefit for using these agents in the adjuvant setting. Pazopanib was tested in the PROTECT trial (A Study to Evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma), in which a total of 1538 patients with resected locally advanced RCC were randomly assigned to pazopanib or placebo for 1 year.<sup>37</sup> The 800-mg starting dose of pazopanib was lowered to 600 mg owing to drug toxicity attrition. The results of the primary DFS analysis of pazopanib at 600 mg showed no benefit over placebo in the adjuvant setting. However, secondary analysis suggests that PROTECT might have been a positive study if the trial had managed to persist with an 800-mg starting dose.<sup>38</sup> In ATLAS (Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients), a phase 3, randomized, double-blinded trial, axitinib was compared with placebo in patients who had locoregional RCC and were at risk for recurrence following nephrectomy. No significant difference in DFS was determined, as the trial was deemed futile during a preplanned interim analysis and was ultimately stopped.<sup>39</sup>

EVEREST/SWOG 0931 (Everolimus for Renal Cancer Ensuing Surgical Therapy, a Phase III Study), the only trial to date to explore adjuvant therapy with a mammalian target of rapamycin (mTOR) inhibitor, was a double-blinded randomized trial of everolimus (Afinitor, Novartis) vs placebo in patients who had undergone nephrectomy. The accrual target had to be increased after enrollment was completed owing to a higher-than-expected dropout rate. The results of this only trial to evaluate an mTOR inhibitor in the adjuvant setting are awaited.<sup>40</sup> The recently reported E3210 trial of adjuvant pazopanib vs placebo in metastatic RCC following resection found no OS benefit from pazopanib.<sup>41</sup>

Two phase 3, multicenter, randomized controlled trials—IMmotion010 (A Study of Atezolizumab as Adjuvant

**Table 2.** Trials of Adjuvant Therapy in RCC

Study	Therapy	Patients, No.	DFS	OS
ASSURE <sup>37</sup>	Sunitinib	647	Median 5.8 y, HR=1.02, <i>P</i> =.8038	HR=1.17, <i>P</i> =.17
	Sorafenib	649	Median 6.1 y, HR=0.97	HR=0.98, <i>P</i> =.85
	Placebo	647	Median 6.6 y, <i>P</i> =.7184	
S-TRAC, all patients <sup>36</sup>	Sunitinib vs placebo	Total: 615 306 vs 309	6.8 vs 5.6 y, HR=0.76, <i>P</i> =.03 median 6.2 y	HR=1.014, <i>P</i> =.938
S-TRAC, higher risk per UISS: T3 with high Fuhrman grade $\geq 2$ and PS $\geq 1$ , or T4, or N1	Sunitinib vs placebo	194 vs 194	Median 6.2 vs 4.0 y, HR=0.74, <i>P</i> =0.04	Not reported
PROTECT <sup>39</sup>	Primary analysis	Total: 1134		
	Pazopanib (ITT) 600- mg dose	571	HR=0.862, <i>P</i> =.1649	HR=0.791, <i>P</i> =.1566
	Placebo	564	Median not attained	
	All patients (ITT) Pazopanib vs placebo	Total: 1538 769 vs 769	HR=0.802, <i>P</i> =.0126	HR=0.823, <i>P</i> =.1570
ATLAS <sup>41</sup>	Axitinib vs placebo	363 vs 361	HR=0.87, <i>P</i> =.32	Not reported
E2810 <sup>43</sup> (resected metastases)	Pazopanib vs placebo	Total: 129	HR=0.85, <i>P</i> =.47, favors pazopanib	HR=2.65, <i>P</i> =.05, favors placebo

DFS, disease-free survival; HR, hazard ratio; ITT, intention-to-treat population; OS, overall survival; PS, performance status; UISS, UCLA Integrated Staging System; y, years.

Therapy in Participants With Renal Cell Carcinoma at High Risk of Developing Metastasis Following Nephrectomy) and KEYNOTE-564 (Safety and Efficacy Study of Pembrolizumab as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy)—are currently assessing the performance of anti-programmed death ligand 1 (anti-PD-L1) and anti-programmed death 1 (anti-PD-1) antibodies, atezolizumab (Tecentriq, Genentech) and pembrolizumab (Keytruda, Merck), respectively, in patients at high risk for metastasis following nephrectomy. Endpoints include DFS and OS. At present, the choices for a patient with high-risk localized RCC are active surveillance vs a risk/benefit discussion of adjuvant sunitinib therapy or clinical trial participation. Overall, vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) therapy has yielded modest efficacy, at best, in the postoperative therapy of localized RCC. The role of immune therapy is still under evaluation. Perhaps progress in biomarker utility will enable a more stringent patient selection based on tumor characteristics and reveal a robust benefit.

## Management of Advanced/Metastatic RCC

Immunotherapy strategies against kidney cancer have demonstrated efficacy for several decades, emerging as powerful weapons for the treatment of metastatic RCC. Conventional cancer treatments are being integrated with immunotherapeutic agents, and a radical transformation of cancer treatment is taking place.<sup>44</sup> Before the advent of immunotherapeutic agents, metastatic RCC was typically addressed with IL-2 or IFN- $\alpha$  because RCC is highly resistant to chemotherapy.<sup>45</sup>

### *Role of Cytoreductive Nephrectomy in Metastatic RCC*

When cytokine-based therapy with IFN attained a more pronounced role in the treatment of metastatic RCC, the question arose of whether CN would add clinical benefit. CN is surgical removal of the primary renal tumor in the setting of metastatic RCC (Table 3). The hypothesis was that patients undergoing debulking surgery would derive increased benefit from cytokine therapy.<sup>46</sup> SWOG 8949 (A Randomized Comparison of Nephrectomy Followed

**Table 3.** Trials of Cytoreductive Nephrectomy in Advanced RCC

Study	Therapy	Patients, No.	RFS/OS
SWOG 8949 <sup>48</sup>	Nephrectomy/interferon	121	Med OS 11.1 mo, $P=.05$
	Interferon	120	Med OS 8.1 mo
EORTC-3047 <sup>47</sup>	Nephrectomy/interferon	42	Med TTP 5 mo, HR=0.6 Med OS 17 mo, HR=0.54
	Interferon	43	Med TTP 3 mo, med OS 7 mo
CARMENA <sup>58</sup>	Nephrectomy/sunitinib	226	Med OS 13.9 mo, HR=0.89, 95% CI 0.71-1.1
	Sunitinib	224	Med OS 18.4 mo
SURTIME <sup>60</sup>	Nephrectomy/sunitinib	50	PFR 42%, median OS 15 mo, HR=0.57, $P=.03$
	Sunitinib/nephrectomy	49	PFR 43%, median OS 32.4 mo

HR, hazard ratio; med, median; mo, months; OS, overall survival; PFR, progression-free rate; RFS, relapse-free survival; TTP, time to progression.

by Interferon Alpha 2-b vs. Interferon Alpha 2-b Alone in Patients With Advanced Renal Cell Carcinoma) from the Southwest Oncology Group and EORTC-3047 from the European Organisation for Research and Treatment of Cancer were phase 3 randomized controlled trials with outcomes that supported the practice of CN plus cytokine therapy with IFN- $\alpha$  in advanced RCC. OS benefit was demonstrated in both trials. DFS improvement was noted in patients who underwent CN before cytokine therapy vs patients who underwent immunotherapy alone with IFN- $\alpha$ .<sup>47,48</sup> SWOG 8949 evaluated 241 patients and showed a 3-month median OS benefit in the nephrectomy group vs the non-nephrectomy group (11.1 vs 8.1 months, respectively). An updated analysis of the trial at a median follow-up of 9 years demonstrated prolonged long-term OS, further supporting the role of nephrectomy before IFN- $\alpha$  in metastatic RCC.<sup>49</sup> In EORTC-3047, a comparable benefit was seen in patients who underwent CN followed by IFN- $\alpha$ . A median OS duration of 17 vs 7 months (hazard ratio [HR], 0.54; 95% CI, 0.36-0.97;  $P=.03$ ) proved to be significantly better in the patients who underwent CN.<sup>47</sup> A meta-analysis of the SWOG and EORTC data showed an OS of 13.6 months among patients who underwent CN plus IFN- $\alpha$  vs 7.8 months among those treated with IFN- $\alpha$  alone, representing a 31% relative reduction in risk for death.<sup>50</sup> In addition, an analysis of 5372 patients with metastatic RCC from the Surveillance, Epidemiology, and End Results (SEER) database demonstrated a significant survival benefit for CN, with a 10-year OS rate of 12.7% among patients who underwent CN vs 1.2% among those without surgery.<sup>51</sup> As a result of these analyses, the role

of CN was correctly established at the time as standard therapy for patients with metastatic RCC. This dogma has changed completely in the setting of targeted VEGFR TKI therapy.

#### ***Targeted Therapy and Role of Nephrectomy in Metastatic RCC***

Molecularly targeted therapy has been a game-changing item in the repertoire for the treatment of metastatic RCC. These agents have not only better efficacy but also better tolerability than do their predecessors in cytokine therapy. These drugs have rapidly gained wide application and have drastically improved outcomes in patients with advanced disease. Up to 10 agents have become available since 2006, which broadly fall into 2 distinct mechanistic categories: VEGF-based therapies, such as sorafenib, sunitinib, pazopanib, axitinib, and the anti-VEGF monoclonal antibody bevacizumab (Avastin, Genentech), and mTOR inhibitors, such as temsirolimus and everolimus.<sup>52-56</sup> These agents have been approved by the FDA for the treatment of metastatic RCC owing to their role in improving progression-free survival (PFS) and, in some studies, OS.

The role of CN with targeted therapy was supported by a meta-analysis that included 39,953 patients across 12 studies and found a reduced risk for death (HR, 0.46; CI, 0.32-0.64;  $P<.01$ ) among patients who were treated with CN and targeted therapy compared with those who received targeted therapy alone.<sup>57</sup> In addition, it is noteworthy that sunitinib as a stand-alone treatment regimen for intermediate- to poor-risk metastatic RCC

demonstrated noninferiority to nephrectomy followed by sunitinib in the recently published randomized phase 3 CARMENA trial (Clinical Trial to Assess the Importance of Nephrectomy).<sup>58</sup> Noninferiority was seen with regard to the primary endpoint of OS (stratified HR for death, 0.89; 95% CI, 0.71-1.10; upper boundary of the 95% CI for noninferiority,  $\leq 1.20$ ). The median OS was 18.4 months in the sunitinib-alone group and 13.9 months in the nephrectomy/sunitinib group. No significant differences in response rate or PFS were observed, and adverse events were as anticipated in each group. A subgroup analysis of patients in the intermediate group, who had a prognosis of less than 12 months from diagnosis to metastasis, showed that CN may benefit this group.<sup>59</sup> This trial shows that many people with advanced RCC can avoid nephrectomy without any loss of survival. In fact, CN has the potential to be detrimental, given that approximately 20% of the patients had severe complications and were not able to receive systemic therapy with sunitinib. The SURTIME trial (Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer) investigated whether a period of sunitinib therapy before CN improves outcome compared with immediate CN followed by sunitinib.<sup>60</sup> Although deferred CN did not improve disease-related outcomes at 28 weeks, the deferred approach enabled more patients to receive sunitinib, and OS outcomes were favorable. The researchers concluded that pretreatment with sunitinib may identify patients with inherent resistance to systemic therapy before planned CN. Recent advances in systemic therapy and FDA approval of immune therapy-based regimens owing to demonstration of superior efficacy compared with sunitinib has again raised the question of the role and timing of CN in the management of synchronous advanced RCC.

### ***Immune-Based Regimens in RCC***

CheckMate 214 (Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma) compared the combination regimen of nivolumab (Opdivo, Bristol-Myers Squibb) and ipilimumab (Yervoy, Bristol-Myers Squibb) with sunitinib therapy, and an OS benefit was noted for the immune therapy.<sup>61</sup> Of note, the Southwest Oncology Group has proposed a study to define the role of surgery in the presence of metastatic disease. EVEREST/SWOG 1931 has been designed to help determine the effect of surgery in the context of nivolumab plus ipilimumab. The design proposes randomization to a control arm of standard therapy with nivolumab/ipilimumab vs a novel arm of nivolumab/ipilimumab (maximum of 4 cycles) followed by CN. Both arms would receive consolidation nivolumab every 4 weeks (Figure).

In addition to nivolumab plus ipilimumab, other immune-based therapies outperformed sunitinib in various studies designed for patients with metastatic RCC. A randomized, phase 3 clinical trial demonstrated significant improvement in OS and PFS with the anti-PD-1 agent pembrolizumab plus the TKI axitinib vs sunitinib, the previous standard of care for metastatic RCC. The median PFS was 15.1 months (range, 12.6-17.7) for pembrolizumab/axitinib and 11.1 months (range, 8.7-12.5) with sunitinib.<sup>62</sup> With the combination, a 31% reduction in the risk for disease progression (HR, 0.69; 95% CI, 0.57-0.84;  $P=.0001$ ) and an OS benefit were observed. Similarly, a combination of avelumab (Bavencio, EMD Serono/Pfizer) and axitinib showed superior efficacy in regard to response rate and PFS in comparison with sunitinib.<sup>62,63</sup>

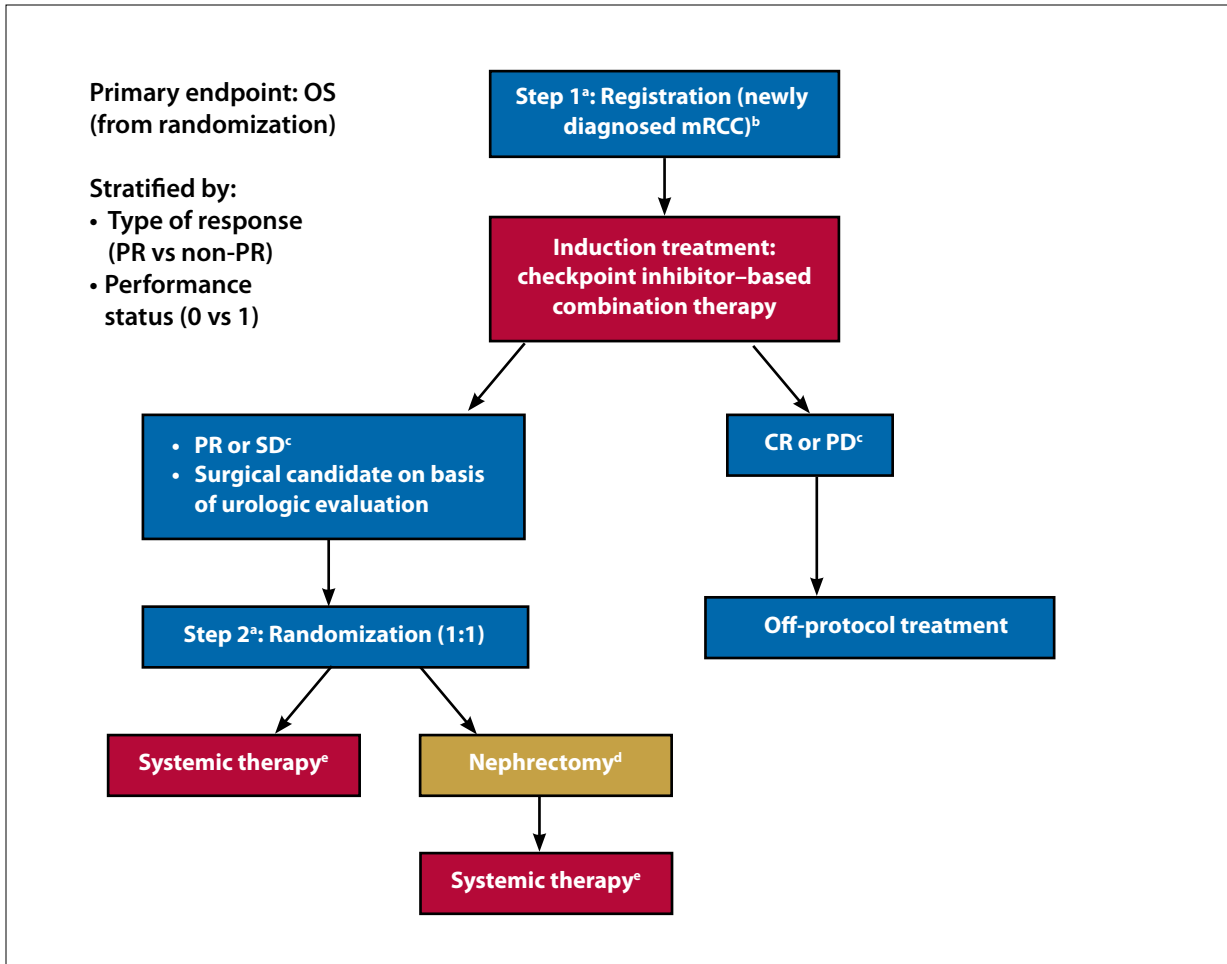
Current trials further exploring the benefits of targeting therapy in metastatic RCC include ADAPTeR (A Study of Anti-PD1 Therapy as Pre- and Post-operative Therapy in Metastatic Renal Cell Cancer). This is a phase 2, single-arm study that is seeking to clarify whether a combination of preoperative and postoperative nivolumab is safe and effective and has an effect on immune modulation in patients with advanced RCC.

### ***Neoadjuvant Therapy in RCC***

Few studies have looked at neoadjuvant therapy in renal cancer. In regard to metastatic disease, one study compared early CN with targeted therapy vs deferred CN with targeted therapy and revealed that the latter approach had more favorable outcomes.

For patients with locally advanced kidney cancer or sarcomatoid renal cancer, the advent of improved results of systemic therapy with nivolumab plus ipilimumab has made it imperative to start with systemic therapy.<sup>64</sup> Local therapy can be considered after a favorable response to systemic therapy has been obtained. For patients with non-clear cell histology, however, initial surgical resection should be considered owing to the suboptimal efficacy of systemic therapy in this condition.

Neoadjuvant therapies with VEGFR TKIs have been evaluated in patients with localized or locally advanced RCC. The results of these endeavors have been unimpressive, and these agents do not appear to enhance surgical or clinical outcomes. Therefore, this approach has not gained favor in clinical management in the context of VEGFR TKIs.<sup>65</sup> However, because of the theoretical possibility of the better efficacy of immune therapy owing to the principle of antigen spread and increased neoantigen load with the primary tumor in place, a contemporary perioperative study with nivolumab has been designed.<sup>66</sup> The EA8143 trial, also known as PROSPER (A Phase 3 Randomized Study Comparing Perioperative Nivolumab



**Figure.** SWOG 1931, also known as PROBE, is a proposed phase 3 randomized trial of immunotherapy-based combination with or without cytoreductive nephrectomy for newly diagnosed advanced/metastatic renal cell carcinoma.

<sup>a</sup>Two opportunities for study entry: before and after treatment initiation.

<sup>b</sup>All histologies except collecting duct carcinoma.

<sup>c</sup>Response based on baseline scan (between 6 wk before start of induction and 2 wk after start of induction) and post-induction scan. Post-induction scan: after 2 or more doses of immunotherapy, 8 to 16 wk after baseline scan, within 6 wk of randomization.

<sup>d</sup>Nephrectomy within 8 wk of randomization.

<sup>e</sup>Systemic therapy may be held for up to 8 wk before nephrectomy. Recommendation: systemic treatment should be held no more than 12 wk during the perioperative period.

CR, complete response; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell carcinoma; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; wk, weeks.

vs. Observation in Patients with Localized Renal Cell Carcinoma Undergoing Nephrectomy), is randomly assigning patients with localized renal cancer (T2-T4, N1, M0) to nephrectomy alone as standard therapy or to neoadjuvant nivolumab for 2 doses followed by nephrectomy and continued nivolumab for a maximum duration of 12 months. Multiple studies have evaluated

neoadjuvant systemic therapy with the goals of downstaging the disease and increasing the likelihood of being able to perform nephron-sparing surgery.

Small studies with sorafenib, sunitinib, and pazopanib revealed modest response rates that made it possible to undertake nephron-sparing surgery or convert unresectable tumors to operable ones, but a lack of effect



on relapse-free survival or OS. No pathologic complete responses were noted. On the basis of these findings, enthusiasm for a neoadjuvant approach with TKI therapy for localized tumors is limited at present. Immune therapy, however, has shown the potential to achieve better outcomes with the primary tumor in place, and studies of neoadjuvant therapy are ongoing.

The management of patients with RCC and inferior vena cava tumor thrombus presents a huge challenge. A small series of 25 patients reported a response rate of 44% (11/25) with sunitinib therapy, but no lasting effect on clinical outcomes was noted.<sup>67</sup> Another series of 48 patients undergoing thrombectomy and RN revealed a relapse-free survival rate of 20%.<sup>68</sup> The sample size was too small to recommend this strategy strongly, and none of the studies reported have been conducted in conjunction with contemporary systemic therapy. Given the modest overall benefit in outcomes with surgical thrombectomy, initial systemic therapy appears to be a reasonable therapeutic consideration.

## Conclusion

With the advances in options for systemic therapy in RCC, the role of surgery is also evolving. Adjuvant therapy with sunitinib after surgery can be considered in high-risk RCC and has FDA approval. Clinical trials of neoadjuvant and adjuvant therapies should be strongly considered. Nephrectomy, or nephron-sparing surgery if feasible, remains standard in localized RCC. Noninvasive procedures such as cryotherapy and RFA can be considered with appropriate patient selection. In advanced or metastatic disease, initial therapy should be systemic targeted or immune therapy, or a combination thereof. The role of CN needs to be explored further.

## Disclosures

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