INTRODUCTION

Renal cell carcinoma (RCC) occurs in approximately 80,000 new patients each year. Of these newly diagnosed cases, 30% of patients may present with metastatic disease. These metastatic disease cases account for the majority of deaths, with approximately 15,000 deaths each year [1]. Surgery (i.e., partial or radical nephrectomy) is the primary treatment option for localized RCC. Historically in the metastatic setting, surgical resection of the primary tumor was also an integral part of treatment, showing benefit in some cases with spontaneous regression of metastatic sites after nephrectomy [2]. However, with the implementation of immunotherapy (IO) and targeted agents, management of metastatic kidney cancer has evolved. The results of more recent trials (e.g., CARMENA and SURTIME) have begun

In patients with renal cell carcinoma (RCC), the use of immunotherapy (IO) and tyrosine kinase inhibitor (TKI) regimens has proven beneficial in treating metastatic disease. These advances have led to the evaluation of IO/IO and IO/TKI treatment combinations in the perioperative setting. Neoadjuvant systemic therapy can improve surgical outcomes for patients by shrinking the tumor and prior studies have shown that the use of TKI regimens reduced tumor size significantly, whereas IO monotherapy had less of an objective radiographic response. In a retrospective series, patients with locally advanced RCC treated with IO/TKI experienced a higher decrease in median tumor size than those treated with IO/IO. For patients with locally advanced bulky tumors or tumor thrombus involving renal vein or inferior vena cava, early systemic treatment may be beneficial (with several trials ongoing). Finally, pembrolizumab has also improved outcomes in the adjuvant RCC setting. These studies have opened the door to other perioperative studies. Using perioperative therapies can alter the course of RCC with neoadjuvant therapies (IO/TKI) facilitating surgical challenges and adjuvant therapy (IO) improving disease-free survival, but trials are in the process and will further evaluate the impact of these treatments. In the meantime, these systemic therapies can be discussed with patients for perioperative treatment of locally advanced and invasive RCCs.
to question the utility of cytoreductive nephrectomy [3,4]. These studies showed that cytoreductive nephrectomy may only be beneficial in a subset of patients and that upfront systemic therapy may be preferred to select appropriate surgical candidates. Given the efficacy of IO and tyrosine kinase inhibitor (TKI) regimens, these combinations are now used in locally advanced tumors in both the neoadjuvant and adjuvant settings.

Several IO-based regimens have been compared to sunitinib and have demonstrated considerable improvement in clinical outcomes. For example, the CLEAR trial randomized patients with metastatic clear cell RCC (ccRCC) to either lenvatinib plus pembrolizumab or sunitinib, and patients had improved objective response rate (ORR) of 71.0% versus 36.1% and median progression free survival of 23.9 months versus 9.2 months (hazard ratio, 0.47; 95% confidence interval, 0.38–0.57) [5]. Similarly, in Keynote 426, axitinib with pembrolizumab improved ORR to 59.3% compared to 35.7% with sunitinib [6]. While the IO/IO combination of ipilimumab/nivolumab has also extended median survival rates, the ORR with IO/IO is less pronounced, around 39% for nivolumab and ipilimumab compared to 32% for sunitinib in the intention to treat population and more significantly seen in the IMDC (International Metastatic renal cell carcinoma Database Consortium) intermediate/poor risk patient population (42% vs. 27%) [7]. Importantly, these efficacy differences in IO/IO versus IO/TKI have shaped the perioperative use of these treatments.

**NEOADJUVANT THERAPY IN NEPHRECTOMY**

Neoadjuvant systemic therapy in localized or locally advanced tumors can improve the challenges of nephrectomy. In patients with large tumors, this may allow changes in surgical approach from radical to partial nephrectomy or downsizing an inferior vena cava (IVC) tumor thrombus to make surgical resection less complicated. Additionally, undergoing upfront surgery may be less tolerable for some patients who have systemic symptoms, where upfront systemic therapy may improve subsequent surgical outcomes. Several studies have demonstrated response to TKIs alone. One historic trial used sunitinib 37.5 mg daily prior to nephrectomy and found a median reduced tumor cross-sectional area of -27.9% [8]. A higher dose (50 mg) of sunitinib also demonstrated a similar reduction in tumor diameter with a -28% reduction in patients with ccRCC but a 1.4% increase in non-clear cell tumors [9]. The toxicities noted with sunitinib were most commonly gastrointestinal related, although in the latter trial, 2 of 30 patients experienced grade 4 toxicity (myocardial infarction and neutropenia) and in the former trial, 1 of 20 patients had grade 4 toxicity (hyponatremia) [8,9]. Axitinib also demonstrated a tumor response when administered in the preoperative setting when given as a 5 mg twice a day dose for several months prior to resection [10,11]. With axitinib, the most common adverse event was hypertension, which could be well-managed with medication. One last trial also demonstrated responses for patients treated with pazopanib [12]. Common adverse events with pazopanib included hypertension and elevated liver enzymes without any grade 4 or 5 adverse events. In all studies, surgical resection was felt to be feasible; adverse events related to surgical resection included urine leak, acute blood loss during the perioperative period and delayed bleed, chylosus ascites, pleural injury, and need for dialysis. However, these were single arm trials and thus hard to assess the true difficulty of surgical resection compared to a non-pretreatment arm.

The response rates with neoadjuvant IO monotherapy have been less pronounced compared to TKIs. Carlo et al. [13] reported on the feasibility of nivolumab prior to nephrectomy in patients at high risk for recurrence and showed little response in the primary tumor. In another similar study by Gorin et al. [14], most patients undergoing upfront IO therapy also demonstrated minimal response. Additionally, there are significant toxicities associated with administration of IO. In the first study, 2 patients had discontinued therapy due to immune related adverse events (irAEs) and in the second study, 2 patients experienced grade 3 events. Treatment of irAEs may also require administration of corticosteroids, which may lead to wound healing complications in the perioperative setting.

Combinations of IO/TKI have also shown efficacy when administered in the neoadjuvant setting. The first IO/TKI combination to be given in the neoadjuvant setting was a
trial by Bex et al. [15], in which patients treated with axitinib and avelumab had median downsizing of 20% and at a median follow-up of 23.5 months, recurrence occurred in 32% of patients with 3 deaths. However, while there is some efficacy in reducing primary tumor size, the survival benefit is unknown without more follow-up.

In the cooperative group PROSPER study by Allaf et al. [16], where one dose of nivolumab was given prior to surgery followed by 9 doses after surgical resection, no recurrence free survival benefit was seen when compared to nephrectomy followed by observation. In a retrospective comparison between IO/IO regimens and IO/TKI regimens, the IO/TKI regimens seem to have higher primary tumor reduction.

In our center, our practice has been to treat patients with locally advanced tumors with IO/TKI combinations. One such patient who had an IVC thrombus was treated with lenvatinib and pembrolizumab with a complete pathologic response (Fig. 1). In our center’s retrospective cohort of 65 patients, those treated with IO/TKI regimens had a median tumor size reduction of 3.3 cm compared to reduction of 1.9 cm for those treated with IO/IO regimens. Patients with IVC tumor thrombi also experienced greater downstaging with IO/TKI regimens than with IO/IO combinations [17]. The current use of upfront systemic therapy is likely center-specific and depends on a multidisciplinary team with coordinated treatment approaches.

**NEoadjuvant therapy for IVC tumor thrombus**

Ongoing trials in our institution are primarily focused on downsizing of tumor thrombus in the IVC. Based on retrospective analysis of locally advanced and metastatic RCC patients that underwent preoperative IO/IO or IO/TKI regimens, IO/TKI regimens demonstrated greater IVC tumor downstaging. This has led to the creation of several clinical trials. One of these is currently enrolling with administration of neoadjuvant lenvatinib and pembrolizumab in patients with IVC tumor thrombus prior to surgery (NCT05319015).

Additionally, early phase trials have shown the safety of stereotactic ablative radiotherapy of 40 Gy in 5 fractions followed by surgical resection [18]. Freifeld et al. [19] showed a favorable safety profile for patients undergoing stereotactic radiation (SAbR) for IVC tumor thrombus in 15 patients, with 58% demonstrating a radiographic response. There are also current ongoing trials that use SAbR in metastatic RCC prior to cytoreductive nephrectomy. In this situation, when compared to untreated archival controls, tumors that were pretreated with SAbR showed increased expression of tumor antigens, which could perhaps provide evidence for the immunomodulation effect of radiation.

While there is evidence to demonstrate favorable tumor responses in the neoadjuvant setting with the use of radiation or systemic therapy, data supporting overall survival benefit is still immature. Use of neoadjuvant therapy may improve the ability to perform nephron sparing surgery or simplify complicated nephrectomy cases. Further studies and ongoing trials will help determine if there is any survival advantage with neoadjuvant systemic therapy.

**Adjuvant Therapy**

In the adjuvant setting, 4 recent trials have reported...
outcomes on patients with high risk of recurrence treated with IO. The KEYNOTE-564 trial randomized patients to a year of adjuvant pembrolizumab versus placebo within 3 months of surgical resection or metastasectomy (for those who had metastatic disease within a year of nephrectomy) and found 37% reduction in risk of recurrence at 30-month follow-up in patients treated with adjuvant IO, as well as ultimately an overall survival benefit at 48-month follow-up [20]. This positive result led to the U.S. Food and Drug Administration approval of pembrolizumab as adjuvant treatment for patients with RCC who have an intermediate or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions [21].

This trial supporting the use of adjuvant pembrolizumab is in contrast with 3 negative adjuvant trials which did not show a clinical benefit in delaying disease recurrence. The PROSPER trial, as mentioned above, was stopped early due to inefficacy and did not show improved disease-free survival. When 6 months of nivolumab plus ipilimumab was compared with placebo in the CheckMate 914 trial, there was also no improvement seen in disease recurrence. Finally, IMMOTION010 was a multicenter randomized phase III trial investigating adjuvant atezolizumab, an anti-programmed death-ligand 1 (PD-L1) inhibitor, in patients at high risk of recurrence following surgery [22]. Disease-free survival was not different between patients receiving IO and placebo. 18% of patients who received IO had a serious adverse event. The RAMPART trial combining durvalumab, also a PD-L1 inhibitor, and tremelimumab, a CTLA-4 inhibitor, is currently ongoing [23]. This trial has coprimary endpoints of disease-free and overall survival and may clarify the true benefit of adjuvant IO in high-risk RCC.

Future directions may include technologies or risk calculators to help select patients most likely to benefit from adjuvant therapy. One method may be augmented with minimal residual disease assays to select outpatients to either escalate or de-escalate treatment. These assays, including circulating tumor DNA, may detect minimal residual disease after surgical resection, and may help with treatment selection. The question remains if these patients would derive greater benefit with IO/IO or IO/TKI therapy rather than IO alone in these adjuvant trials.

**CONCLUSIONS**

In conclusion, using systemic treatments with proven benefits for metastatic RCC in the earlier perioperative and adjuvant settings can steadily change our management paradigms in localized and locally advanced RCC. Pre-operative systemic therapies can impact the disease course and the ability to surgically resect some tumors. In the adjuvant setting, for now pembrolizumab is the only approved IO therapy which has shown to improve disease-free survival, especially in high-risk patient populations (T3/T4, sarcomatoid, N1, M1 no evidence of disease, etc.). In clinical practice, it is vital to have shared decision making with patients to discuss the risks and benefits of adjuvant systemic therapy in the context of toxicities, disease recurrence benefit, and cost. Further trials are ongoing to solidify the role of perioperative systemic treatments in RCC.

**NOTES**

- **Author Contribution:**
  Conceptualization: TZ; Data curation: N/A; Formal analysis: N/A; Methodology: N/A; Project administration: N/A; Visualization: N/A; Writing - original draft: IT, TZ; Writing - review & editing: IT, QQ, JT, WI, JC, VM, TZ.
- **ORCID**
  Isamu Tachibana: https://orcid.org/0000-0002-0950-1296
  Qian Qin: https://orcid.org/0000-0003-0653-8920
  Jacob Taylor: https://orcid.org/0000-0003-2190-7309
  Wadih Issa: https://orcid.org/0000-0002-3239-9875
  Vitaly Margulis: https://orcid.org/0000-0002-5837-4561
  Tian Zhang: https://orcid.org/0000-0001-8914-3531

**REFERENCES**


