Neoadjuvant Therapy for Locally Advanced Renal Cell Carcinoma

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KEYWORDS

• Neoadjuvant therapy • Targeted therapy • Immune checkpoint inhibitor • Renal cell carcinoma • Locally advanced • Nephrectomy • Partial nephrectomy

KEY POINTS

- Currently, no level 1 evidence exists to support the use of neoadjuvant therapy for locally advanced renal cell carcinoma.
- Proposed benefits of neoadjuvant therapy include tumor downsizing to facilitate resection or nephron-sparing and -shrinking renal vein thrombi.
- Multiple ongoing phase I/II trials are investigating immune checkpoint inhibitors along with combination therapy.
- Outside of a clinical trial and exceptional clinical scenarios, there is no role for routine neoadjuvant therapy use. It may have utility in patients with absolute indications for partial nephrectomy or unresectable disease.

INTRODUCTION

In 2018, there were an estimated 403,262 cases of kidney cancer diagnosed world-wide.[1] Although the incidence of early stage disease has increased, up to 40% of patients still present with locally advanced (≥cT3 and/or N1) or metastatic disease.[2] Renal cell carcinoma (RCC) is inherently chemotherapy resistant with an overall response rate (ORR) of just 5.6% to cytotoxic agents.[3] Based on randomized control trials showing improved survival compared with interferon alone, nephrectomy has been the treatment of choice for both locally advanced and metastatic disease.[4,5] Although surgical resection is the only definitive cure for RCC, recurrence rates may exceed 60% among the highest-risk patients.[6,7] However, before 2006 the available therapies were highly toxic with low efficacy and thus had little role in the perioperative setting.[8,9] After the US Food and Drug Administration approved sunitinib, a small molecule tyrosine kinase inhibitor (TKI), for cytokine-refractory metastatic RCC (mRCC) there was renewed interest in perioperative systemic therapy.[10] Subsequent trials in both the adjuvant and neoadjuvant space have been conducted, culminating in the 2018 approval of sunitinib for adjuvant therapy among high-risk patients with clear cell RCC (ccRCC).[11]

In RCC, the Von-Hippel-Lindau tumor suppressor gene is commonly mutated. This leads to persistence of hypoxia inducible factor and subsequent overtranscription of vascular endothelial growth factor (VEGF), ultimately resulting in stimulated angiogenesis.[12,13] The development of agents targeting the VEGF pathway and other pathways ushered in the targeted therapy (TT) era and new interest in preoperative therapy. Targeted therapies include TKIs (sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, and lenvatinib), mammalian target of rapamycin inhibitors

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(everolimus, temsirolimus), and bevacizumab, an anti-VEGF monoclonal antibody. To date, most published studies on presurgical therapy have used TT agents.

In 2015, nivolumab, an immune checkpoint inhibitor (ICI) targeting PD-1, was approved as second-line therapy for mRCC after demonstrating an ORR of 25% in CheckMate-025.[14] ICIs target immune cell-specific regulatory pathways such as PD-1/PD-L1, and CTLA-4, promoting antitumor immunity. In recent trials, ICIs have shown ORR of 37% to 59%, leading to both single agent and combination approvals in the metastatic setting.[15–18] In addition, with combination therapy, complete response (CR) rates have ranged from 5% to 9%.[15–18] Thus, current trials are now evaluating these agents in the perioperative setting.

Importantly, early presurgical therapy trials often contained two subsets of patients: those with no evidence of metastatic disease (M0) for whom therapy was *neoadjuvant* and those with metastatic disease (M1) for whom therapy was considered *pseudoneoadjuvant* or *presurgical*.[19] Pseudoneoadjuvant therapy may serve as a litmus test to identify patients who may not benefit from cytoreductive nephrectomy (CN), a strategy with support from multiple phase II trials, and hypothesis-generating results from SURTIME trial and posthoc analysis of the CARMENA trial.[20–22]

METHODS

PubMed, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched with keywords including "neoadjuvant, renal cell carcinoma, nephrectomy, targeted therapy, immune checkpoint inhibitors, mammalian target of rapamycin inhibitors, and tyrosine kinase inhibitors." Publications were included if they included patients with localized RCC. Articles with language other than English, editorials, and case reports were excluded.

The existing literature consists of case series, retrospective single and multiinstitution analyses, and small prospective phase I/II single arm clinical trials. Only a single prospective randomized clinical trial has been completed.[23] Objective measures used to assess tumor response to neoadjuvant therapy include Response Evaluation Criteria in Solid Tumors (RECIST) criteria and RENAL nephrometry score.[24] By RECIST, the ORR is a combination of the complete response (CR) rate and partial response (PR) rate, defined as at least a 30% decrease in the sum of diameters of target lesions.[24] Subjective assessments based on objective data include ability to resect previously unresectable disease, ability to perform partial nephrectomy, and alteration in surgical approach.

In terms of safety and tolerability, drug toxicity is recorded using the Common Terminology Criteria for Adverse Events (CTCAE) and complications using the Clavien-Dindo Classification system.[25]

RATIONALE FOR NEOADJUVANT THERAPY

Given the high recurrence rates with locally advanced disease, rationale for neoadjuvant therapy includes both improvement in oncologic outcomes (recurrence-free survival or overall survival [OS]) as well as facilitation and improving risk profile of complex resections.[26] Neoadjuvant therapy may eradicate micrometastatic disease, thus decreasing recurrence rates and improving overall survival.[21,27] Others hypothesize that with the tumor in situ, proangiogenic and/or proimmunogenic factors may enhance the efficacy of targeted therapy.[28] Likewise higher disease burden may promote systemic inflammation and greater immune system activation.[28]

Neoadjuvant therapy may facilitate the resection of surgically complex tumors, allowing unresectable tumors to become resectable and decrease the need for adjacent organ resection. For those with imperative indications for renal preservation, it may allow for an organ-sparing approach and facilitate patient recovery if minimally invasive surgery can be performed.[26,29] Finally, in the case of inferior vena cava (IVC) tumor thombi, therapy may theoretically shrink the tumor thrombus, decreasing surgical morbidity and/or reduce the need for major vascular resection.

OUTCOMES OF NEOADJUVANT THERAPY STUDIES

High-Risk Localized Renal Cell Carcinoma

To date, there are no randomized trials that evaluate the impact of neoadjuvant therapy on oncologic outcomes. In the adjuvant setting, the S-TRAC trial demonstrated a benefit of sunitinib in improving progression-free survival (PFS) but no benefit for OS.[11] Other trials in the adjuvant setting including ASSURE, PROTECT, and ATLAS have shown no benefit.[30–32] Given the limited efficacy demonstrated in the adjuvant setting with targeted therapy, a randomized neoadjuvant trial investigating survival outcomes may be difficult to conduct.[19]

Tumor Downsizing

Table 1 summarizes the reported response rates in prospective perioperative therapy trials that include locally advanced, M0 patients.

Table 1
Summary of prospective neoadjuvant clinical trials

Study, Year	N	Agent	Dose	Duration	Discontinuation Before Surgery	Inclusion Criteria	Median % Decrease in Diameter[a] (Range %) cm Decrease in Diameter	PR by RECIST	PN/RN
Hellenthal,[36] 2010	20	Sunitinib	37.5 mg PO QD	3 mo	5 d: N = 5 24 h: N = 15	≥cT1bNanyMany ccRCC M1: 20%	Mean: 11.8% (27% - +11%)	5%	8/12
Cowey,[33] 2010	30	Sorafenib	400 mg PO BID	Median: 33 d (8–59)	24–48 h	≥cT2NanyMany M1: 43%	9.6% (40% - +16%) 0.8 cm	7%	0/30
Silberstein,[37] 2010	12[b]	Sunitinib	50 mg PO QD[c]	12 wk	2 wk	cTanyNanyMany ccRCC Indication for NSS M1: 41%	Mean: 21.1% (45% - 3.2%) 1.5 cm	16%	14/0
Rini,[38] 2012	28	Sunitinib	50 mg QD	6–120 wk	≥ 7 d	cTanyNanyMany Unresectable M1: 63%	22% (100% - +13%) 1.2 cm	25%	9/4
Karam,[40] 2014	24	Axitinib	5 mg BID	12 wk	36 h	cT2-T3N0M0 ccRCC	28.3% (42.9% - 5.3%) 3.1 cm	46%	5/19
Rini,[35] 2015	25	Pazopanib	800 mg PO QD	8–16 wk	≥ 7 d	cTanyNanyM0 ccRCC Indication for NSS	26% (43% - +2%) 1.5 cm	36%	20[d]/8
Lebacle,[41] 2018	18	Axitinib	5mg PO BID[e]	8–32 wk	6 d	cT2aN0M0 ccRCC	17% (29.4% - 4.8%) 1.2 cm	22%	16/1[f]
Hatiboglu,[23,g] 2017	12	Sorafenib	400 mg PO BID vs placebo	4 wk	24 h	cT1-3N0M0	29% (61% - 4.9%) 1 cm	44% vs 0%[h]	4/5 1/2

[a] Positive numbers (increase in size) bolded.
[b] 14 kidneys, 2 patients with bilateral disease.
[c] 6 wk cycle: 4 wk on, 2 wk off.
[d] 17 patients, 3 bilateral partials (n = 20 total PN).
[e] Allowed up titration.
[f] 1 patient did not undergo surgery.
[g] RCT: 3:1 Sorafenib versus Placebo.
[h] Inferred from Fig 2, Hatiboglu et al, 2017.

In 2010, Cowey and colleagues[33] administered sorafenib to 30 patients with stage II or higher renal masses, of whom 56% had locally advanced disease (the remainder were M1). Median reduction in tumor diameter was 9.6% and only 4% had a PR based on RECIST criteria.[33] They also evaluated masses using the modified Choi criteria and found a median decrease in intratumoral enhancement of 13%, potentially representing radiographic tumor necrosis.[34]

Multiple studies, both prospective and retrospective, have evaluated the efficacy of presurgical sunitinib in a locally advanced and/or metastatic population.[23,33,35,36] Among 4 prospective series, the median decrease in tumor diameter ranged from 11.8% to 22%, with a PR rate of 7% to 37% among studies reporting RECIST criteria.[33,36–38] Importantly, none reported PD during treatment. Among retrospective series, Lane and colleagues[39] published the largest, composed of 72 patients and enriched with nonmetastatic locally advanced disease (n = 60). Treatment with sunitinib resulted in a 32% reduction in tumor area with 19% of patients experiencing a PR.[39] In addition, they reported that clear cell histology, low Fuhrman grade, and lack of lymph node disease were associated with better radiographic response.[39]

Other TKIs prospectively evaluated include pazopanib, axitinib, and sorafenib.[23,35,40,41] The only prospective randomized control trial was conducted by Hatiboglu and colleagues[23] in which 12 patients were randomized 3:1 to either sorafenib or placebo. The sorafenib arm demonstrated a median tumor reduction of 29% and 4 of 9 had a decrease in RENAL nephrometry score.[23] Rini and colleagues[35] conducted a phase II trial of pazopanib given to 25 patients with nonmetastatic disease. They reported a median tumor decrease of 26%, PR rate of 32%, and decrease in RENAL nephrometry score of 36%.[35]

Two prospective phase II trials using neoadjuvant axitinib have been published.[40,41] The first was by Karam and colleagues,[40] in which 24 patients with cT3aN0M0 disease received up to 12 weeks of neoadjuvant axitinib. They demonstrated a 28% decrease in tumor diameter with a median RENAL nephrometry score change from 11 to 10.[40] A second study was published by Lebacle and colleagues[41] in 2019. Among this cohort of patients with T2aN0M0 disease, they reported a 17% reduction in tumor size and 66% downstaging rate.[41]

Changing Unresectable to Resectable

The first published report of presurgical therapy was in 2008 by Van der Veldt and colleagues.[42] In their retrospective report of 17 patients with mRCC given 4 weeks of sunitinib, 3 of 10 tumors initially deemed unresectable were able to be surgically removed.[42] Thomas and colleagues[26] treated 19 patients with unresectable disease with 50 mg of sunitinib daily for 4 weeks. Sixteen percent of patients had a PR by RECIST.[26] The median tumor size reduction was 24% and 21% (4/19) eventually underwent nephrectomy.[26] Likewise, Bex and colleagues[43] retrospectively identified 10 patients in whom CN was deferred due to "doubtful resectability" in the setting of metastatic disease. Three of the ten patients underwent successful CN after downsizing of the primary site and response in the metastatic sites to sunitinib.[43] Initially, all 3 patients had evidence of liver invasion, which was confirmed histologically at the time of resection—thus despite downsizing there was no downstaging.[43]

In a prospective phase II trial, Rini and colleagues[38] administered sunitinib 50 mg daily in patients with biopsy confirmed unresectable RCC. Twenty-nine patients, 66% with metastatic disease, met the definition of unresectable—large tumor (7%), bulky lymphadenopathy with vessel encasement (31%), venous thrombosis (21%), and/or proximity to vital structures(41%).[38] Thirteen patients (45%) met the primary endpoint, surgical resection, of whom 9 underwent partial nephrectomy and 4 underwent radical nephrectomy.[38] The investigators conclude that the modest decrease in tumor size (1.3 cm) may affect surgical approach in specific clinical contexts, such as partial versus radical nephrectomy in a patient with a hilar tumor and solitary kidney.[38] However, the ability to remove a large tumor with bulky nodes is not likely to be enhanced by sunitinib.[38]

In summary, a locally advanced tumor deemed unresectable in the absence of metastatic disease is rare. Although neoadjuvant therapy may decrease the tumor diameter, it is unlikely to affect surgical planning in large, bulky disease.

Converting from Radical to Partial Nephrectomy

The utility of neoadjuvant therapy to allow for partial as opposed to radical nephrectomy has also been explored. Patients with bulky bilateral tumors, locally advanced disease in a solitary kidney, or with compromised renal function have been hypothesized to benefit from nephron-sparing surgery (NSS).[37] Silberstein published a retrospective review and prospective pilot of the utility of sunitinib in this setting. Twelve patients (14 renal units), 5 with metastatic disease, who had complex tumors (collecting

system abutment, hilar vessel invasion) received sunitinib and subsequently underwent successful NSS.[37] Of the 14 renal units, 3 developed urine leaks, which healed with conservative management.[37]

Lane published a retrospective review of 72 patients (78 renal units) who received presurgical sunitinib at 4 centers.[39] The indication for therapy was for bulky/central renal tumors not amenable to partial nephrectomy (PN) (60%) or patients with mRCC having a low relative volume of disease in the primary tumor (40%).[39] The median nephrometry score decreased from 10% to 9% and 63% of patients underwent PN, including 76% of nonmetastatic patients.[39]

Rini and colleagues[35] conducted a prospective phase II trial of 8 to 12 weeks of pazopanib among 25 patients with locally advanced ccRCC requiring maximal preservation of renal parenchyma. Patients were eligible if radical nephrectomy (RN) or PN would yield GFR less than 30 mL/min/1.73 m^2 and/or there was an anticipated increased risk of morbidity with PN due to high complexity (RENAL score: 10–12) or hilar tumor location.[35] The primary endpoint was completion of NSS and secondary endpoint was the amount of vascularized parenchyma that could be preserved compared with pretherapy assessment.[35] Based on surgeon assessment, partial nephrectomy was not feasible before therapy in 13/25 patients due to tumor anatomy.[35] Six of these thirteen patients ultimately underwent NSS (46%), and the amount of functional parenchyma spared increased from 107 to 173 cc.[35] For all other patients who had an imperative indication for renal preservation, the amount of parenchyma spared increased from 178 to 204 cc.[35] Five of seven patients who underwent RN required eventual dialysis as did one patient who underwent PN.[35] Among the 20 PN performed, there were 5 urine leaks (25%).[35]

McDonald and colleagues[44] conducted a multiinstitutional retrospective review comparing outcomes of patients with imperative indication for PN (n = 125) who received neoadjuvant therapy (n = 47) with those who did not (n = 78). A total of 29.8% of patients who received sunitinib experienced CTCAE grade 3 or higher toxicity.[44] They found that the low-grade 30-day complication rate was higher in the neoadjuvant group (P = .042), but there was no difference in high-grade complications (P = .73).[44] Likewise they reported no difference in positive margin rates or renal function.[44] On multivariable analysis, receipt of neoadjuvant therapy did not predict long-term renal function outcomes.[44] Thus, the investigators conclude that for complex tumors neoadjuvant therapy before PN does not negatively affect long-term outcomes.[44]

AXIPAN was a multiinstitutional phase II trial of neoadjuvant axitinib for patients with cT2 ccRCC and normal renal function.[41] The primary endpoint was downsizing of cT2 tumors to less than 7 cm so that PN could be performed according to standard of care.[41] Patients were deemed not eligible for PN by the treating surgeon and tumor board review.[41] The primary outcome was the percentage of patients receiving PN for cT1 renal mass after no more than 6 months of therapy.[41] A total of 18 patients were enrolled, with a median tumor size of 7.6 cm and RENAL score of 11.[41] Following treatment, median tumor size decreased to 6.4 cm and RENAL score to 10.[41] Overall, 67% (12/17) of patients met the primary endpoint and of the 17 who underwent surgery, 16 had a PN.[41] Notably, 11% of patients had a positive margin and 22% had developed metastatic disease at 2-year follow-up, attributable to the high proportion of pT3a (41%) and high-grade (47%) tumors.[41]

In summary, in patients with complex tumors and imperative indication for renal preservation (solitary kidney, bilateral disease) there may be a role for neoadjuvant therapy to facilitate PN. However, surgical approach is subjective, and the literature should be interpreted carefully.[45] Karam and colleagues[45] retrospectively reviewed imaging studies following neoadjuvant axitinib treatment to determine PN feasibility pre- and posttherapy. Among 5 independent reviewers, the odds of PN feasibility markedly increased after axitinib, but they were not able to identify which patients were more likely to benefit from axitinib based on their pretreatment scans.[45] In addition, interobserver agreement was higher for moderately complex tumors as compared with more complex tumors, which is the more clinically relevant group.[45]

Downstaging Inferior Vena Cava Thrombus

In locally advanced or metastatic disease, the presence of a tumor thrombus may increase surgical risk, with the level of the tumor thrombus correlating with perioperative complication rates, which range from 12% to 47%.[46] Thus, interest in neoadjuvant therapy to decrease thrombus level and potentially decrease surgical morbidity has been explored in several series.[47–50]

The first, by Cost and colleagues,[50] described 25 patients who received targeted therapy (sunitinib = 12, other = 13) for IVC thrombus (levels II–IV). Overall, 44% had a decrease in height (median 1.5 cm decrease), 28% increase in height, and 28% stable height.[50] There was minimal change

in thrombus level—84% had stable thrombi, 12% had a decrease in thrombi level, and 4% had an increase in thrombus level.[50]

Bigot and colleagues[47] reported similar findings to Cost in a series of 14 patients treated with TT (sunitinib = 11, sorafenib = 3). In this cohort, 7% (n = 1) were downstaged, 84% were stable, and 1 patient was upstaged.[47] Overall, 43% had a decrease in thrombus height (median decrease −2 cm), 43% remained stable, and 14% had an increase in thrombus length.[47] Kwon and colleagues[48] evaluated 22 patients (sunitinib = 18, sorafenib = 4) using both RECIST and Choi criteria. They reported that 40.9% of patients achieved a partial response based on Choi criteria (decrease in size of at least 10% or decrease in attenuation of at least 15%), and this was independently associated with improved overall survival.[48] Only 2 (9%) of the patients had a PR using RECIST criteria. However, the application of this study is limited in surgical populations as the investigators did not include information related to surgical tumor thrombus levels.[48]

More recently, Field and colleagues[49] published a large multiinstitutional study comparing 51 patients who underwent either primary resection (n = 34) or neoadjuvant therapy (sunitinib) followed by surgery (n = 19). In the neoadjuvant group, they report a mean reduction in thrombus length of 25% (1.3 cm).[49] Overall, 42.1% of patients had a decrease in thrombus level, whereas 52.6% had stable thrombus level, with 27.8% experiencing a PR according to RECIST.[49] Although those who received neoadjuvant treatment had significantly lower operative blood loss, there were no other differences in surgical outcomes, including surgical approach (open vs minimally invasive) between the 2 groups.[49] Although the investigators report improved cancer-specific and all-cause mortality in the neoadjuvant group (47.1% vs 10% [P = .007] and 52.9% vs 21.1% [P = .024] respectively), this was driven by the patients who were M1 at presentation.[49] On subgroup analysis of those without metastatic disease, there was no survival difference.[49]

Although neoadjuvant therapy may decrease the size of the primary tumor, presurgical targeted therapy does not seem to have the same impact on tumor thrombus. Although Field and colleagues[49] report better response than prior studies (possibly due to uniform receipt of sunitinib), there was no impact on surgical approach or outcomes. Although they demonstrated an oncologic survival benefit for presurgical therapy, this was not seen in the true neoadjuvant group.[49] Ultimately, given the lack of significant thrombus shrinkage, there is little evidence that neoadjuvant targeted therapy use has an impact on surgical approach and thus is of limited value.

CONCERNS WITH NEOADJUVANT THERAPY

Multiple concerns related to neoadjuvant therapy have been raised, including increased wound healing complications, increased surgical complications, drug toxicity or adverse events, and risk of disease progression with surgical delay. There was significant concern regarding safety and wound healing after Jonasch and colleagues[21] reported 21% of patients treated with presurgical bevacizumab had wound dehiscence or delayed healing. However, Cowey noted no wound-related issues with sorafenib, potentially attributable to its shorter half-life.[33] Subsequently, in a 2012 trial with sunitinib, Rini also reported no wound complications.[38] Likewise, neither Karam or Rini and colleagues[35,40] noted significant wound-related issues with axitinib or pazopanib, respectively.

Chapin and colleagues[51] retrospectively compared patients with synchronous mRCC who either underwent immediate CN or received presurgical therapy followed by CN. Although no differences were found in severe or overall complications in the 12 months after surgery, patients who received presurgical therapy were significantly more likely to have delayed (>90 days) wound complications, superficial wound dehiscence, and wound infection (odds ratio 4.14, 95% confidence interval: 1.6–10.6, P = .003).[51] Harshman and colleagues[52] found that presurgical TKI use increased the incidence of intraoperative adhesions (86% vs 58%, P = .01) among 14 patients compared with matched controls, but did not affect overall complications, bleeding, or wound healing.

Complications among prospective neoadjuvant target therapy trials are outlined in **Table 2**. There is inconsistent reporting, with not all studies using the standardized Clavien-Dindo system. However, Silberstein reported 21.4% (3/14) of patients experienced a urine leak as did 25% of the patients who received pazopanib in the trial by Rini and colleagues[35,37] To date, no data evaluating the surgical safety of ICI in the neoadjuvant setting have been published.

Grade 3 or higher CTCAE drug toxicities are also shown in **Table 2**. Approximately 30% to 80% of patients experienced grade 3 or higher toxicity. However, these generally resolved with either dose reduction or drug discontinuation.[23,33,35,36,38,40,41] In addition, Karam and colleagues[40] evaluated quality of life during the neoadjuvant therapy and found that

Table 2
Summary of complications and adverse events in prospective neoadjuvant clinical trials

Study, Year	% CTCAE Grade 3 or Higher AE	Description of Adverse Events	Dose Modifications	≥ Clavien-Dindo Grade 3 Complications	Wound Complications
Hellenthal et al,[36] 2010	40%	Grade 3: 35% Neutropenia: 10% Hand-foot: 10% Pancreatitis: 15% Grade 4: 5% Hyponatremia	Interruption: 25% Dose reduction: 10%	Not formally reported	None
Cowey et al,[33] 2010	30% (Grade 3)	Grade 3 Rash, acneiform: 13.3% Hand-foot: 6.6% Fatigue: 3.3% Headache: 3.3% Hypertension: 3.3%	Dose reduction: 33%	Not formally reported	Superficial wound breakdown: 1 (POD 8)
Silberstein et al,[37] 2010	NR	NR	NR	Not formally reported *Urine leak: 21.4%*	None
Rini et al,[38] 2012	7% (Grade 4)	Grade 3/4[a] Dermatologic: 14% Mucositis: 3% Thrombocytopenia: 21% Fatigue: 10% Diarrhea: 7% Anorexia: 3% Bleeding: 3% Hypertension: 34% Neutropenia: 14% Anemia: 10%	NR	Not formally reported	None
Karam et al,[40] 2014	79% (Grade 3)	Grade 3 Hypertension: 41.7% Fatigue: 4.2% Oral mucositis: 4.2% Hand-foot syndrome: 4.2% LFT elevation: 8.3% Abdominal pain: 8.3% AKI: 4.2% Thrombocytopenia:4.2%	Discontinuation: 8.3% (11, 7 wk)	Grade 3: 8.3% Chylous ascites: 4.2% Bleeding: 4.2%	Superficial wound complication: 4.2%

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Table 2
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Study, Year	% CTCAE Grade 3 or Higher AE	Description of Adverse Events	Dose Modifications	≥ Clavien-Dindo Grade 3 Complications	Wound Complications
Rini[35] 2015	64% (Grade 3)	Grade 3 Fatigue: 8% Elevated LFTs: 20% Hypertension: 36% Thrombocytopenia: 4%	NR	Grade 3: 8% Stent for urine leak: 5% Angioembolization: 5% Urine Leak: 25%	Wound infection: 8%
Lebacle et al,[41] 2018	27.7% (Grade 3)	Not provided Serious adverse event (11.1%) Impaired condition: 5.5% Polycythemia: 5.5%	Dose reduction: 5.5% Discontinuation: 16.7%	Overall: 28% *Grade 3:* 16.6% Embolization: 5.6% Urine leak: 11.2% *Grade 4*: 5.6% Suicide attempt *Grade 5:* 5.6% MI	None
Hatiboglu et al,[23] 2017	66%[b] (Grade 3)	Grade 3[c] Hand-foot syndrome: 44.4% Hypertension: 11.1% Serious adverse event: 11.1% Generalized exanthema	Dose reduction: 66% Discontinuation: 11%	Grade 5: 5.5% MI (death): placebo	None

Abbreviations: AE, adverse events; AKI, acute kidney injury; LFT, liver function test; MI, miocardial infarction; POD, postoperative day.
[a] 2 Grade 4: MI, neutropenia.
[b] Calculated based on sorafenib arm (n = 9) only.
[c] Complication detail not fully recorded.
Data from Refs.[23,33,35–38,40,41]

quality of life was significantly decreased at week 7 compared with baseline (P = .0004) but had returned to baseline by week 19 (P = .3).

Another concern with the use of neoadjuvant therapy was the risk of progressive disease (PD) among nonresponders. PD may be attributed to the documented rebound phenomenon, due to early revascularization or tumoral edema following TKI discontinuation.[53,54] Although no studies reported PD during neoadjuvant treatment, in an analysis of 66 patients who received 2 to 3 cycles of sunitinib, Powles reported that 36% of patients experienced PD during the 4-week wait before CN.[55] Similarly, they reported that 26% of patients experienced PD during a phase II trial evaluating presurgical pazopanib in the mRCC setting, again highlighting the importance of surgical timing.[56] Given that these reports are in the metastatic setting, they may not be applicable to the neoadjuvant setting.

In summary, although it seems safe to delay surgery to administer neoadjuvant therapy, most patients do experience some degree of drug toxicity, which typically resolves with dose reduction or drug discontinuation. Those who undergo partial nephrectomy may have a higher risk of urine leak, although given the small sample sizes, it is not possible to control for other confounding variables. Although there were some reports of increased wound complications related to TT, overall complication rates are equivalent. However, it remains to be seen whether this will be true with the newer ICI agents.

PREDICTING RESPONSE TO NEOADJUVANT THERAPY

Limited data exist regarding factors that predict response to neoadjuvant therapy for localized or locally advanced RCC. Investigations regarding predictors of tumor response performed in the metastatic setting have been generally extrapolated to the neoadjuvant setting; however, these findings require actual validation in the nonmetastatic setting.

Among patients treated with tyrosine kinase inhibitors, Voss et al evaluated associations between survival and mutation status of select genes of interest commonly mutated in RCC (PBRM1, STED2, KDM5C, BAP1, TP53, and TERT).[57] They demonstrated that the mutational status of BAP1, PBRM1, and TP53 were independently prognostic among patients with advanced or mRCC treated with 1st line TKIs.[57] Beuselinck et al previously performed ccRCC transcriptome analysis and identified four ccRCC subtypes (ccrcc1-4) with varying responses to sunitinib therapy.[58] Lower response rates and shorter PFS/OS were identified among ccrcc1 and ccrcc4 tumors compared to ccrcc2 and ccrcc3 tumors.[58]

The development of checkpoint inhibitors has led to a significant effort to identify biomarkers for tumor response; however, no validated predictive markers currently exist. The degree of PD-L1 expression has been evaluated with differing results. The Javelin Renal 101 trial demonstrated improved PFS among mRCC patients receiving axitinib with avelumab compared with sunitinib in both the PD-L1 positive tumors as well as in the overall population.[18] Similarly, CheckMate 214 demonstrated that among patients with mRCC, PD-L1 expression greater than or equal to 1% had an objective response rate of 58% compared with the objective response rate for PD-L1 expression less than 1% of 37% after exposure to nivolumab/ipilimumab.[17] This trial also demonstrated that OS and PFS was improved for nivolumab/ipilimumab compared with sunitinib regardless of PD-L1 expression level.[17] Tumor mutational burden and characterization of the tumor infiltrating lymphocytes have also been evaluated as potential predictors of response to checkpoint inhibitors. Overall, these biomarkers are limited as a predictive biomarker given the heterogeneity of expression in the primary tumor and unclear cutoffs that define positivity.[59] Future investigations will require not only identifying effective neoadjuvant therapies but also biomarkers that may predict success.

OUR CURRENT PRACTICE

At our center, we only use neoadjuvant therapy (i.e. limited to non-metastatic patients) in few selected situations. First: in the setting of a neoadjuvant clinical trial (the most common scenario). Second: when a patient has a solitary kidney, with a large tumor that is not felt to be amenable to partial nephrectomy safely (either from an oncologic perspective, or from a functional renal remnant perspective). Third: when a patient has a large tumor with local invasion into adjacent organs (cT4) in the setting of sarcomatoid RCC. Fourth: in the setting of “unresectable” disease, which is the least common scenario. In all these situation, we always consult our Interventional Radiology colleagues to perform percutaneous image-guided core biopsies to establish the histologic subtype and diagnosis, and to obtain specimens for research when indicated.

FUTURE DIRECTIONS

With the approval of ICI for use in mRCC, there has been interest in evaluating these drugs in the

Table 3
Summary of ongoing clinical trials of neoadjuvant therapy in locally advanced renal cell carcinoma

NCT Trial #	Agent	Phase	N	Dose	Duration (Weeks)	Inclusion[a]	Primary Outcome(s)	Status[b]	Est. Completion
Neoadjuvant Phase I/II trials for locally advanced renal cell carcinoma									
NCT01361113[64]	Pazopanib	II	21	800 mg QD	8	• T2a-T4NanyM0	ORR → 38.1%	Completed	1/2015
NCT02575222[68]	Nivolumab	I	30	3mg/kg q2W	6	• T2a-T4NanyM0 • TanyN1M0	Safety[c]	Active, not recruiting	6/2020
NCT02595918[67]	Nivolumab	I	29	IV q2W	8	• Resectable, high risk M0 • M1 undergoing CN or meta-stasectomy	Feasibility to receive at least 3 doses without significant surgical delay[d]	Recruiting	4/2021
NCT02762006[66]	Durvalumab & Tremelimumab	Ib	45	Durvalumab x 1 Or Durvalumab & Tremelimumab x 1[e]		• T2b-4 NanyM0 • TanyN1M0 • Any histology	Dose limiting toxicity	Active, not recruiting	11/2020
NCT04028245[61] *SPARC-1*	Spartalizumab & Canakinumab	I	14	Spartalizumab: 300 mg q4w x 2 doses Canakinumab: 400 mg IV q4w x 2 doses	8	• T2-T4N0M0 • TanyN1M0	% who proceed to RN within 6 wks	Recruiting	12/2021
NCT03438708[65] *PADRES*	Axitinib	II	50	5mg BID[f]	8–10	• TanyNanyM0 with imperative indication for NSS	• % reduction of longest diameter in mm • ORR • Δ in R.E.N.A.L. score • PN feasibility	Unknown[g]	2/2020
NCT04022343[62]	Cabozantinib	II	17	60 mg QD[h]	12	• T3-T4NanyM0 • TanyN1M0 • Unresectable	ORR	Recruiting	08/2023

NCT04118855[69]	Axitinib & Toripalimab	II	30	Axitinib: 5 mg BID Toripalimab: 3 mg/kg q3w x3	12	• T2-T3N0M0	ORR	Open, not recruiting	3/2026
NCT03341845[71] *NeoAvAx*	Axitinib & Avelumab	II	40	Axitinib: 5 mg BID Avelumab: 10 mg/kg q2W	12	• Int/high risk locally advanced RCC	Partial remission	Recruiting	1/2025
NCT03680521[70]	Sitravatinib & Nivolumab	II	25	Sitravatinib QD x 2 wk then with nivolumab 240 mg IV q2W	6–8	• Locally advanced RCC	ORR	Recruiting	4/2020
Thrombus Trials									
NCT02473536[63]	SABR	I/II	30	8Gy/5Frac or 12 Gy/3Frac		• ≥ level II IVC tumor thrombus, surgically resectable • Any Histology	Phase 1: safety[i] Phase 2: RFS	Active, not recruiting	12/2024
NCT03494816[60] *NAXIVA*	Axitinib	II	20	5mg BID[j]	8	• T3a-NanyMany	Improvement in Mayo Classification	Recruiting	6/2020

[a] Limited to ccRCC unless otherwise specified.
[b] As of 06/2020.
[c] Any CTCAE adverse event from initial dose through 100 d post-surgery.
[d] Significant surgical delay defined as ≥112 d after first nivolumab dose.
[e] Both arms include multiple cohorts with varying adjuvant dosages.
[f] Allows for dose escalation as tolerated.
[g] Recruiting as of 12/2019; unknown as of 06/2020.
[h] Two dose reductions allowed.
[i] 90 d Grade 4 to 5 adverse events attributable to SABR.
[j] Allows for dose escalation.

neoadjuvant setting with or without the addition of TKIs. **Table 3** lists the active clinical trials as of October, 2019. Currently, there are 8 open trials investigating neoadjuvant therapy in nonmetastatic RCC and 2 that are closed and awaiting results.[60–71] One, NCT01361113, which evaluated Pazopanib in a phase II trial among localized ccRCC, recently reported an ORR of 38.1%.[64] The primary endpoint for most of the phase II trials is ORR alone, with the exception of PADRES (NCT03438708).[65] This multicenter study of neoadjuvant axitinib is limited to patients with complex renal masses and imperative indication for nephron preservation.[65] In addition to ORR, the study aims include ability to perform partial nephrectomy and avoidance of renal replacement therapy.[65] In addition, there are also 2 open evaluating neoadjuvant therapy for IVC thrombi.[60,63] NCT02473536 is a combined phase I/II trial of stereotactic ablative body radiation for greater than or equal to level 2 tumor thrombi, whereas NAXIVA (NCT03494816) is evaluating the response of tumor thrombi to axitinib.[60,63]

SUMMARY

There is limited data to support the use of neoadjuvant therapy outside of a clinical trial. Neoadjuvant TT for tumor downsizing alone is of limited benefit for bulky, unresectable tumors and has shown minimal utility in patients with IVC thrombi. In select patients, neoadjuvant therapy may facilitate NSS, but the definitions of "unresectable" or "not amenable to PN" are subjective. A multidisciplinary discussion should be undertaken when considering neoadjuvant therapy, particularly in experienced centers. Future trials will determine whether there is a role for ICI in the neoadjuvant setting.

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