The Potential Role for Neoadjuvant Therapy in Renal Cell Carcinoma

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Abstract: Surgical resection remains the standard of care for clinically localized renal cell carcinoma (RCC). Nearly 1 in 4 patients will have a recurrence after surgery performed with curative intent, and stand to benefit from additional therapy. Currently, no proven adjuvant or neoadjuvant therapies are available. A number of phase 3 adjuvant therapy trials are ongoing that are evaluating small-molecule drugs approved for metastatic RCC. The outcomes of these trials may provide insights for designing future phase 3 neoadjuvant therapy trials. Several phase 2 neoadjuvant trials for RCC have recently been completed or are ongoing. These trials have established the safety and response rates associated with several agents, and will pave the way for future phase 3 trials of neoadjuvant therapy for RCC. Neoadjuvant therapies may be useful for decreasing the risk of recurrence after surgery, maximizing nephron sparing, and evaluating molecular effects of targeted therapies in human tumors.

Keywords
Neoadjuvant therapy, renal cell carcinoma, presurgical therapy, kidney cancer

Renal cancers make up approximately 4% of all malignancies and account for approximately 2% of cancer-related deaths in the United States.[1] In 2013, it is estimated that 65,150 people will be diagnosed with cancers of the kidney or renal pelvis, and approximately 13,680 people will die of their disease. Approximately 34% of patients present with metastatic or regionally advanced kidney cancer.[2]

Renal cell carcinoma (RCC) is the most common malignancy of the adult kidney. Localized RCC is most often treated with surgery, such as a partial or radical nephrectomy.[3] Unfortunately, approximately 23% of patients diagnosed with localized RCC relapse after surgery.[4] Better treatment strategies are therefore needed for patients at highest risk for recurrence.

Neoadjuvant therapy refers to nonsurgical treatment administered prior to surgery for localized cancer. It is a more specific term than presurgical therapy, which can refer to preoperative treatment for both localized and metastatic disease. Neoadjuvant therapy is distinct from adjuvant therapy, which is administered after curative resection of clinically localized disease. This article will focus on systemic

Table 1. Ongoing Phase 3 Randomized, Double-Blind, Placebo-Controlled Trials of Adjuvant Therapy for High-Risk RCC

Trial	ASSURE[12]	EVEREST[17]	SORCE[14]	S-TRAC[13]	PROTECT[15]	ATLAS[16]
ClinicalTrials .gov identifier	NCT00326898	NCT01120249	NCT00492258	NCT00375674	NCT01235962	NCT01599754
Intervention	Sorafenib × 1 year, sunitinib × 1 year	Everolimus × 54 weeks	Sorafenib × 1 or 2 years	Sunitinib × 1 year	Pazopanib × 1 year	Axitinib × 3 years
Accrual target	1923 patients	1218 patients	1656 patients	720 patients	1500 patients	592 patients
Status	Enrollment complete	Recruiting	Recruiting	Recruiting	Enrollment complete	Recruiting
No. of arms	3	2	3	2	2	2
Histologic subtype	Clear or non–clear cell	Clear cell or papillary	Clear or non–clear cell	Clear cell	Clear cell	Clear cell

ASSURE, Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; ATLAS, Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients; EVEREST, Everolimus in Treating Patients With Kidney Cancer Who Have Undergone Surgery; PROTECT, A Study to Evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma; S-TRAC, Sunitinib Treatment of Renal Adjuvant Cancer; RCC, renal cell carcinoma; SORCE, Sorafenib in Treating Patients at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer.

neoadjuvant therapy. At this time, there is no established role for neoadjuvant therapy in RCC. Therefore, we discuss potential opportunities for using neoadjuvant therapies.

Goals of Neoadjuvant Therapy

Neoadjuvant therapies have a well-established role in the treatment of a number of malignancies, such as rectal, laryngeal, and breast cancers.[5] There are several important advantages to neoadjuvant therapy:

Neoadjuvant therapy may reduce the risk of metastatic recurrence. The cornerstone of treatment for clinically localized RCC is surgical resection. However, approximately 23% of patients undergoing surgery for localized RCC have their disease recur[4] owing to micrometastatic disease present at the time of surgery. An effective neoadjuvant therapy has the potential to eradicate micrometastatic disease and enhance the likelihood of curative therapy.

Neoadjuvant therapy may facilitate organ preservation. In cancers of the rectum, larynx, and breast, neoadjuvant therapy can shrink the primary tumor and help preserve the function of critical organs by decreasing the extent of surgical resection. Not only do RCCs occur in an organ that performs a critical function, but many patients with RCC have preexisting renal insufficiency. Therefore, neoadjuvant therapies capable of downstaging renal tumors may maximize nephron sparing during surgery.

Neoadjuvant therapy can be used to understand drug mechanisms and identify biomarkers. Having a clear understanding of a drug's mechanism of action in human tumors is critical in optimizing therapy, developing strategies to overcome drug resistance, and nominating biomarkers for predicting treatment response.

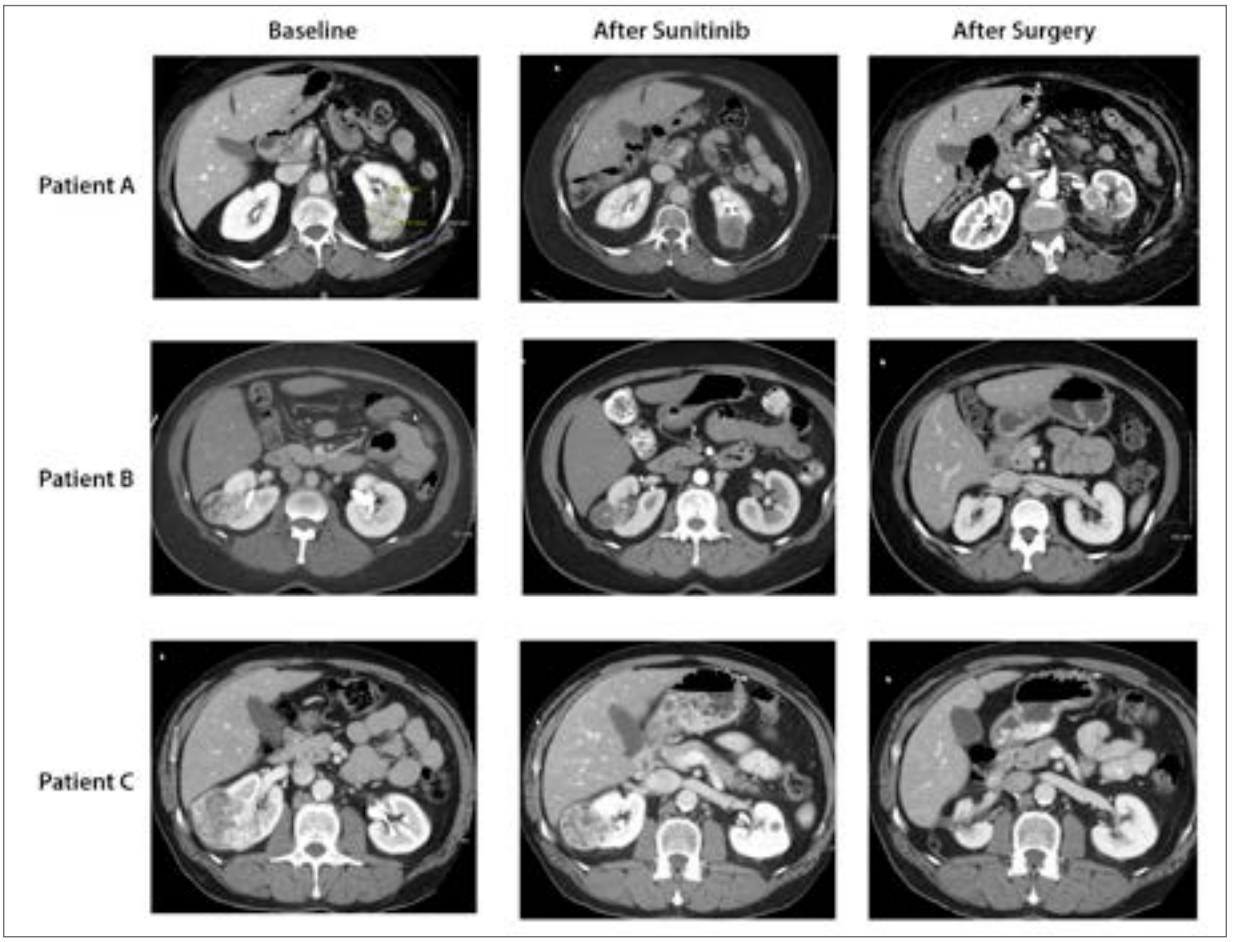
Neoadjuvant Therapy to Reduce Risk Recurrence

Both adjuvant and neoadjuvant approaches may reduce the risk of recurrence after surgery. Currently, there are no established adjuvant therapies for RCC. However, several large adjuvant therapy trials are underway (Table 1). An analogous neoadjuvant trial would be resource-intensive and require a large number of patients. Several unanswered questions pose challenges when designing a definitive neoadjuvant trial. What agent is most promising? What is the optimal treatment duration? What tumor subtypes should be included? How should clinicians identify high-risk patients? What is the role of the diagnostic biopsy? Is surgery safe after neoadjuvant therapy?

There is currently no empirical evidence that neoadjuvant therapy can lead to better survival than adjuvant therapy. Therefore, it is reasonable to wait for the results of ongoing adjuvant therapy trials before designing neoadjuvant trials with survival endpoints. The ongoing adjuvant therapy trials are expected to provide insights on which agents may effectively eradicate micrometastatic disease, and on the necessary length of treatment.

Regardless of the outcomes of the adjuvant studies, neoadjuvant approaches deserve consideration. They have several theoretical advantages over adjuvant therapy. Targeted therapies currently approved for metastatic RCC can decrease the size of primary tumors.[6-8] Therefore, downstaging the primary tumor may facilitate definitive surgical resection and reduce the risk of locoregional recurrence. Neoadjuvant approaches allow patients to immediately start systemic therapy to treat microscopic metastases, which are the lesions most likely to lead to death. In addition, patients may be able to tolerate higher doses of systemic therapy prior to surgery than when they are deconditioned by the surgery and the postoperative recovery.

Figure. Computed Tomography Scans of Patients Treated With Neoadjuvant Sunitinib and Laparoscopic Partial Nephrectomy



Patients with clear cell renal carcinoma were enrolled in a pilot study of presurgical sunitinib. Computed tomography scans were obtained at baseline, after 2 to 3 months of sunitinib, and 2 to 3 months after surgery.

Neoadjuvant Therapy to Facilitate Organ Preservation

The kidneys provide a life-sustaining function. Although normal overall renal function requires just 1 healthy kidney, the patient population that develops RCC has a high incidence of diabetes and hypertension, which can lead to renal insufficiency. Chronic renal disease occurs in approximately 40% of people aged 60 years or older, in more than 40% of people with diabetes, and in 25% of people with hypertension in the United States, based on data from the National Health and Nutrition Examination Survey.[9]

Nephron-sparing surgery, also referred to as partial nephrectomy, therefore plays an important role in the management of small renal tumors, particularly in patients with preexisting renal insufficiency. Larger tumors require radical nephrectomy, and some tumors are borderline resectable by partial nephrectomy. These tumors may be amenable to neoadjuvant therapy to decrease tumor size and facilitate organ preservation. The Figure shows representative computed tomography (CT) images of patients we treated with sunitinib (Sutent, Pfizer) prior to laparoscopic partial nephrectomy as part of a clinical trial.[6] In all 3 examples, patients' tumors decreased in size during treatment with sunitinib, and final resection margins were negative.

Neoadjuvant Therapy to Understand Drug Mechanism and to Identify Biomarkers

In the era of targeted therapies, proposed drug mechanisms can be evaluated using human tumors and modern methods for examining DNA methylation, RNA, and protein expression.[10] After neoadjuvant therapy, there are important molecular endpoints that can be considered:

Target. Small-molecule drugs are designed to interact with specific molecular targets. Therefore, the tumor can be assessed for the presence of the target. This is ideally done on pretreatment biopsy, prior to starting neoadjuvant therapy. However, biopsies may be unreliable for assessing the target. The large amount of tissue from the nephrectomy is well suited for definitively determining the presence of the target and evaluating the heterogeneity of target expression.

Table 2. Contemporary Clinical Trials for Neoadjuvant Therapy for RCC

Center (Identifier)	Drug	Conditions	Duration	Accrual Goal	Primary Endpoint	Status
ARTIC*[23] (NCT01715935)	Everolimus	Localized, mRCC	6 weeks	60 patients	Objective response	Recruiting
University of Toronto[19] (NCT00480935)	Sunitinib	Localized	4 weeks	30 patients	Radiologic response associated with 1 cycle of sunitinib	Recruiting†
University of North Carolina[20] (NCT01361113)	Pazopanib	Localized	12 weeks	56 patients	Objective response	Recruiting
MD Anderson[21] (NCT01263769)	Axitinib	Localized	12 weeks	40 patients	Objective response	Enrollment complete
St Joseph's Healthcare Hamilton[24] (NCT01404104)	Temsirolimus	Localized, mRCC	12 weeks	11 patients	Objective response	Enrollment complete
Cleveland Clinic[7] (NCT00459979)	Sunitinib	Localized, mRCC	Varied	30 patients	Percentage of patients with initially unresectable primary tumors who become resectable after presurgical therapy	Completed, results published
Roswell Park Cancer Institute[6] (NCT00849186)	Sunitinib	Localized, mRCC	90 days	20 patients	Safety of sunitinib; safety of surgery after 90 days of treatment with sunitinib	Completed, results published
University of North Carolina[22] (NCT00405366)	Sorafenib	Localized, mRCC	8 weeks	30 patients	Number of subjects experiencing adverse events while taking sorafenib prior to nephrectomy; feasibility of neoadjuvant systemic therapy prior to nephrectomy	Completed, results published

*Association Pour La Recherche des Thérapeutiques Innovantes en Cancérologie.

†Last updated received by ClinicalTrials.gov in 2011.

mRCC, metastatic renal cell carcinoma.

Target engagement. In traditional drug development, serum drug levels are measured to establish drug pharmacokinetics. However, the doses achieved in the serum may be too low to engage the target or too high to achieve the desired molecular effects. Therefore, molecular effects of target engagement provide the ideal feedback for establishing treatment dose. Examples of molecular markers of target engagement include the phosphorylation status of signaling proteins downstream of the target and the expression signatures of relevant signaling pathways.

Cellular effect. It is possible for a drug to engage its target without leading to an antitumor response because of unintended "off-target" effects, which have the potential to enhance or inhibit the antitumor response. Examples of off-target effects of small-molecule kinase inhibitors include modulation of angiogenesis, inflammation, or host immunity. Therefore, cellular changes can be monitored that are "downstream" of target engagement and immediately "upstream" of clinical response. Examples of such markers of early response include apoptosis, autophagy, and cell division.

Clinical response. Clinical response is a traditional endpoint measured in clinical trials. If treatment duration is sufficiently long, serial imaging may capture clinical response, which can be useful for supervising the molecular analysis from the nephrectomy specimen. However, an important caveat is that potent drugs that produce large clinical responses may generate extensive necrosis and make the tumor ill-suited for assays that require intact macromolecules, such as messenger RNA.

Adjuvant Trials

The state of adjuvant therapies has implications for development of neoadjuvant approaches. Ongoing adjuvant trials focus on commercially available multitargeting tyrosine kinase inhibitors for advanced RCC. These include sunitinib, sorafenib (Nexavar, Bayer and Onyx), pazopanib (Votrient, GlaxoSmithKline), and everolimus (Afinitor, Novartis).[11] Several key phase 3 trials are summarized in Table 1. All these studies include patients at high risk for recurrence after nephrectomy. The ASSURE (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma) trial is a 3-arm study evaluating 1 year of sunitinib, sorafenib, or placebo.[12] The S-TRAC (Sunitinib

Treatment of Renal Adjuvant Cancer) trial is investigating 1 year of sunitinib or placebo for a higher-risk group than the ASSURE trial.[13] The SORCE (Sorafenib in Treating Patients at Risk of Relapse After Undergoing Surgery to Remove Kidney Cancer) trial recently finished comparing 1 or 2 years of sorafenib postoperatively with placebo.[14] PROTECT (A Study to Evaluate Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma) is comparing pazopanib and placebo after nephrectomy.[15] ATLAS (Adjuvant Axitinib Therapy of Renal Cell Cancer in High Risk Patients) is investigating the use of adjuvant axitinib (Inlyta, Pfizer) for 3 years.[16] All these studies use agents that target receptors for vascular endothelial growth factor and platelet-derived growth factor, thus inhibiting angiogenesis. The EVEREST (Everolimus in Treating Patients With Kidney Cancer Who Have Undergone Surgery) study is the only study investigating a mammalian target of rapamycin (mTOR) inhibitor.[17] All of the trials include patients with clear cell RCC; EVEREST also includes patients with papillary RCC, and SORCE also includes patients with non–clear cell RCC.

Neoadjuvant Studies

No large-scale neoadjuvant therapy trials in RCC are ongoing at this time. However, a number of small clinical trials with a variety of endpoints are being conducted (Table 2). A large number of presurgical therapy trials have been conducted in patients with metastatic disease undergoing cytoreductive nephrectomy.[18] These studies help establish the safety of preoperative systemic therapy and surgery after the use of targeted therapies, which are often antiangiogenic agents with the potential to interfere with wound healing.

For localized RCC, 3 phase 2 trials are currently active. A study from the University of Toronto is assessing the radiologic response rate associated with 1 cycle of neoadjuvant sunitinib.[19] A study from University of North Carolina is treating patients with 12 weeks of pazopanib prior to nephrectomy, and is assessing response rate.[20] A study from MD Anderson that has completed enrollment involves treating 40 patients with 12 weeks of axitinib; the primary outcome measure is response rate.[21]

Several studies are enrolling patients with both metastatic and localized RCC, and have endpoints ranging from safety to progression-free survival (Table 2). Several of these studies have been completed, with published results. In a study conducted at the Cleveland Clinic, 30 patients thought to have unresectable RCC were treated with daily sunitinib.[7] Patients were assessed every 12 weeks to determine surgical resectability. The median decrease in size of the primary tumor was 22%. In the study, 45% of patients met the primary endpoint of being considered surgically resectable and underwent nephrectomy. In a study conducted at Roswell Park Cancer Institute, patients with metastatic or large, localized RCC were treated with sunitinib for 3 months prior to surgery.[6] The primary endpoint was safety, and there were no surgical complications attributable to preoperative sunitinib therapy. On imaging obtained after 2 months of sunitinib, the mean cross sectional tumor diameter decreased by 27.9%. After a decrease in tumor size, 8 patients presenting with cT1b tumors underwent successful laparoscopic partial nephrectomy. A study from the University of North Carolina treated 30 patients with preoperative sorafenib and concluded that preoperative sorafenib is safe and feasible.[22] In this study, the median duration of sorafenib therapy was 33 days, which produced a 9.6% decrease in primary tumor size.

Summary

The standard-of-care treatment for clinically localized RCC remains surgical resection. Patients at high risk for recurrence stand to benefit from systemic therapy. A number of phase 3 adjuvant therapy trials are ongoing that are evaluating targeted agents that are active against metastatic RCC. The outcomes of these trials will influence how neoadjuvant approaches are developed for RCC. The potential goals of neoadjuvant therapy include decreasing the risk of disease recurrence, maximizing organ preservation, and evaluating the molecular effects of systemic therapy. The neoadjuvant setting provides an ideal platform for investigating the molecular interactions between drug and tumor to yield insights into mechanisms of action and drug resistance and to provide candidates for predictive biomarkers. Multiple phase 2 neoadjuvant therapy trials are assessing safety and response rate, and will pave the way for any future phase 3 trials of neoadjuvant therapy for RCC.

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