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Challenges in the long-term management of patients with metastatic renal cell carcinoma treated with targeted therapy: Optimizing surgery, systemic therapy and quality of life

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Abstract

Therapy for patients with metastatic renal cell carcinoma is becoming increasingly effective. Sustained partial remissions, occasional complete responses, and manageable quality of life are seen in a subset of individuals. As we face the prospect of generating an increasingly large number of patients requiring long-term management, the choice and timing of systemic therapy and surgical interventions is becoming increasingly important. In this paper, we review the timing and type of cytoreductive nephrectomy, what to do for patients with oligometastatic disease, and how to deal with complete responders. In addition, we summarize the major side effects experienced with the commonly used molecularly targeted agents, and provide guidance on how to maximize benefit from these agents while maintaining an acceptable quality of life for patients. As treatment efficacy improves, the optimal integration of systemic therapy, surgery and toxicity management will become a critical aspect of our care for patients with mRCC.

Keywords

renal cell carcinoma; targeted therapy; cancer survivorship; therapy complications

Introduction

The development of molecularly targeted therapy has changed the treatment paradigm for patients with metastatic renal cell carcinoma [38]. During the past five years, six agents/regimens [20 bevacizumab plus interferon alpha, everolimus and pazopanib] have been approved for the management of patients with advanced RCC [14-16, 23, 35, 36, 39, 41-43]. While targeted agents have in general produced higher response rates, longer progression-free survival or improved overall survival than cytokines, their success is limited due to several factors. First, approximately 20% of patients with mRCC have disease which is refractory to multiple targeted agents, and succumb to their illness fairly quickly. Identification of determinants of disease progression to overcome resistance to targeted therapy, and the development of novel therapeutics for these patients represent a high priority for research in RCC. Second, while the vast majority of patients with mRCC respond to multiple targeted agents given sequentially, continued administration of these agents is often required to maintain a response or stable disease, leading to short-term and

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long term adverse events. Third, despite their initial effectiveness in providing tumor control, targeted agents are not curative, complete response [10, 12, 17, 29, 44] is rare, and a minority of patients survive beyond five years from initiation of therapy.

In this review, we examine the challenges encountered in the long term management of patients with mRCC and provide suggestions for managing them.

Cytoreductive Nephrectomy in Patients with mRCC: For Whom, When and How?

Patients with mRCC face a fairly heterogeneous outcome. As we increase the number of individuals with long-term survival, the consequences of different surgical management approaches are becoming increasingly important.

Cytoreductive nephrectomy [29] became standard of care after two phase 3 trials showed survival benefit in favor of CN followed by interferon alpha (IFN) compared to IFN alone. [17, 33] During the past five years, targeted therapy has displaced cytokines for the treatment of patients with mRCC, based on improved response rates, progression-free survival (PFS) and overall survival [1, 2, 4, 5, 7-13, 18-23, 25, 27-29]. This paradigm shift from cytokines to targeted therapy in the management of patients with mRCC has raised questions regarding the role of CN in the management of patients with mRCC. Is CN still necessary? If it is, what is the optimal timing of CN, and what is the best surgical technique?

At the current time, we do not have any prospective data to specifically guide us on the role of cytoreductive nephrectomy in patients with mRCC who receive treatment with molecularly targeted agents. Nevertheless, it should be noted that in the studies that established the efficacy of targeted agents in mRCC, the majority of patients had undergone cytoreductive nephrectomy prior to receiving systemic therapy. [14-16, 23, 35, 39, 41-43]. In addition, in those studies where relative benefit of targeted agents was assessed as a function of nephrectomy state, ((Motzer, 2007 #2293;Hudes, 2007 #2350), the directionality of benefit was consistently in favor of the targeted agent both for patients who had undergone nephrectomy as well as those who did not. Therefore, at this point in time, cytoreductive nephrectomy remains the standard of care for appropriately selected patients. Who are these patients? As a practical guideline, patients with mRCC and primary in situ who are candidates for CN, as defined by the criteria of the Southwest Oncology Group (SWOG)/European Organization for Radiation and Therapy for Cancer (EORTC) trials should undergo upfront CN unless they are participating in a clinical trial testing the role of presurgical therapy. A close look at the eligibility criteria of the SWOG and EORTC cytoreductive nephrectomy studies reveals that to be eligible, patients were required to have a performance status of 0 or 1, and have evidence of a resectable primary tumor.[17, 33] In addition, very few of those patients had multiple organ sites of metastases. As such, there are no data confirming the benefit of cytoreductive nephrectomy in patients with unresectable primary tumors, widely disseminated disease (as defined by three or more organ sites of disease), non-clear cell histology, multiple bone or liver metastases, or poor-risk features as defined by Memorial Sloan Kettering Cancer Center [34-36] or Heng *et al*'s criteria[21]

What about timing of surgery relative to systemic therapy? At this point in time, we have data showing that pretreatment with antiangiogenic therapy is feasible, relatively safe, and does result in size reduction of primary tumors (Table 1). [2, 10, 11, 13, 27, 32, 40, 43, 46]. Unfortunately, this size reduction is in the order of five to ten percent, and a presurgical treatment strategy with the currently available agents is unlikely to consistently downstage primary lesions. As available therapies improve, this paradigm may shift, and we may be able to consistently perform nephron-sparing kidney surgery. There are data in the nonmetastatic setting that suggest a survival advantage for patients who undergo partial

nephrectomy, when compared to patients who undergo radical nephrectomy [36, 44]. This is likely due to the consequences of nephron loss and worsening renal function. As systemic therapy for mRCC improves outcomes, we will likely face the impact of radical cytoreductive nephrectomy on survivorship. For patients with excellent performance status, good risk features and longer life expectancy, a partial nephrectomy can be contemplated where feasible. In the future, if pretreatment with systemic therapy can consistently downstage the primary tumor, we may permit a larger number of individuals to undergo partial nephrectomy, and possibly face fewer longterm problems arising from lower nephron reserves.

Two randomized phase 3 trials in patients with mRCC who present with primary tumor in situ will attempt to answer some of these questions in the next few years. The CARMENA trial, which has OS as primary endpoint, is recapitulating the design of the SWOG/EORTC trials, by randomizing patients to CN followed by sunitinib versus sunitinib alone, and will ask the question of whether adding cytoreductive nephrectomy to sunitinib treatment is beneficial. The second trial, sponsored by the EORTC, has PFS as primary endpoint and is evaluating the impact of upfront versus delayed nephrectomy in the context of sunitinib treatment. The debate regarding the role of CN in the era of targeted therapy will likely continue until data from these phase 3 trials are available.

Management of the patient with oligometastases and indolent disease

Patients with mRCC who are symptomatic from their cancer require prompt initiation of therapy. These individuals may require local modalities, such as surgery, radiation, thermal ablation or embolization, for the control of threatening or symptomatic disease. On the other hand, there are patients with mRCC who develop tumor recurrence many years after nephrectomy and have low-volume metastasis to lungs, lymph nodes or endocrine organs. Some of these patients may demonstrate an indolent and stable course if observed initially without therapy, and can be followed closely with deferral of systemic therapy. Frontline data on the impact of delayed therapy initiation can be extrapolated from the phase III study randomizing patients between upfront pazopanib versus placebo.[41] Although the progression free survival (PFS) data in this study clearly favored the pazopanib group, initial analysis of the overall survival [1, 2, 4, 5, 7-13, 18-23, 25, 27-31] did reveal a statistically significant difference between arms in this patient population, which was not specifically selected for indolent disease. Similar findings exist in the second- and third-line administration of everolimus versus placebo in patients who were refractory to sunitinib or sorafenib.[36] Although improvements in PFS were observed in the everolimus arm, there was no OS difference between arms. These data suggest that deferral of systemic therapy may be safe in a subset of individuals. A trial formally evaluating this approach will likely contribute to decreasing therapy related morbidity in patients with mRCC.

An alternate strategy is to initiate systemic therapy for a period of time, decrease the number of metastatic lesions to an absolute minimum, and then consider metastasectomy. A large number of retrospective studies have reviewed the role of metastasectomy in patients with metastatic disease, and although uncontrolled, suggest that there may be benefit for patients who can be surgically rendered free of disease.[18, 19, 28, 30, 45] A prospective study reviewed this strategy for patients who were treated with cytokine-containing regimens.[11] Patients who were pretreated with immunotherapy containing regimens for at least four months and demonstrated at least stable disease were enrolled on the trial, and underwent surgical removal of their metastatic deposits, followed by post-surgical consolidative therapy. Patients with lung metastases, and those who were successfully rendered free of disease were those most likely to benefit from this strategy. The potential for perioperative complications in the context of pretreatment with molecularly targeted agents (in particular, antiangiogenic agents) need to be considered as well.

For patients who develop a solitary metastasis after nephrectomy, a reasonable approach is to perform metastasectomy upfront, as some of these patients, especially those with lymph node, endocrine organ site or lung metastasis, have the potential for long-term survival and cure with surgery alone.

Management of the patient who achieves a complete response

A rare but welcome event is the achievement of CR after treatment with targeted therapy. When faced with this situation, do you discontinue systemic therapy altogether, or do you continue therapy at the same dose, or at a lower dose for maintenance until disease recurrence? Very few data exist to guide us for these patients. A questionnaire was sent out to French physicians asking to describe experiences managing mRCC patients who achieved CR while receiving sorafenib or sunitinib.[1] Complete response was reported in 65 pts out of an unknown denominator. Thirty-nine patients achieved CR with therapy alone and 26 underwent local procedures to render them free of disease. The large majority of patients had clear-cell histology (61/65), previous nephrectomy (64/65) and developed CR while on sunitinib (61/65). All but four patients had good- or intermediate-risk criteria. Complete response was achieved in 27 pts, 23 pts and 15 pts with 1, 2 or >2 metastatic sites respectively. Twelve of the 39 pts, who developed CR with receptor tyrosine kinase inhibitors [1, 3, 4, 10, 21, 39] alone, continued TKI after CR, while 27 stopped it at an average of 1 month after CR. For these 27 pts, 17 pts who stopped treatment are still in CR (63%) with a median follow up of 291 days. Among the 26 pts in CR after TKI plus local treatment, 23 pts stopped TKI after CR, and 15 of them are still in CR (65%) with a median follow up of 322 days. A second retrospective analysis was published by Johannsen *et al*, showing that twelve patients out of a 226 patient experience achieved either treatment induced CRs (n=5, all patients received sunitinib) as well as patients who underwent metastasectomy after achieving a PR (n=7).[26] Time to progression in this twelve patient group was six months, with recurrences in both pre-existing and new sites. Patients did respond to a reintroduction of systemic therapy.

Based on outcomes seen in phase III trials, the CR rate while receiving targeted therapy is rare, estimated at less than one percent. [14-16, 23, 35, 36, 39, 41-43] Patient characteristics that permit us to predict whether patients will develop recurrent disease after stopping therapy have not been validated. In general, we will treat patients for three to six months after achieving a CR. At that point an assessment of the patient's side effect profile, prior burden of disease and prior disease growth kinetics are evaluated and used to make a decision on whether or not to stop treatment.

Management of targeted therapy related adverse events

As the use of targeted therapy becomes commonplace and patients receive multiple sequential courses of therapy, the management of toxicities associated with these agents becomes increasingly important. A number of reviews have been published on this subject. [6, 20, 21, 31] Preventing permanent organ damage improves quality of life for individuals with mRCC, and maintains options for receiving subsequent lines of treatment, either on study or off-study. Major toxicities associated with each class of agent are described below, as well as strategies to mitigate these toxicities. A general principal in the management of most of the following side effects is that interrupting therapy to mitigate toxicity and allow recovery of normal tissue homeostasis will in the long run permit more therapy to be administered to the patient, as recovery will be quicker, and patients will be more likely to restart therapy at the same dose. It is important to note that studies have shown, that at least for sunitinib, a higher area under the curve (AUC) of drug is associated with better clinical outcome. [22] Therefore, working with the patient to treat symptoms, minimize dose

reduction, and to maximize the amount of drug given over a defined time period will maximize the potential benefit provided by the agent.

Multi-tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib)—These 3 TKIs have in common the ability to inhibit the VEGF and PDGF receptors and the stem cell factor receptor (c-kit). The main adverse events of these agents include fatigue, diarrhea, rash, hypertension, nausea, mucosal irritation and hand-foot skin reaction.

As a result of VEGF blockade, all of these TKIs produce hypertension and proteinuria. Although the randomized phase 3 trials with sorafenib and sunitinib initially reported hypertension in 20 and 25%, respectively,[14-16, 23, 35] in our experience, the incidence of hypertension secondary to these agents is near 40-50%. Hypertension secondary to pazopanib has been reported to be near 40 %.[41] Proteinuria was reported in less than 10% of patients enrolled on the phase 3 trials with these TKIs, but its incidence in non-study use appears higher, especially in patients who are treated sequentially with these agents (EJ and NT, unpublished observations). Risk factors for the development of high blood pressure during TKI therapy include history of coronary artery disease, age older than 65 years, diabetes mellitus, smoking, dyslipidemia, family history and prior history of hypertension. [24] Retrospective data suggest development of hypertension during TKI therapy in mRCC may be a marker for improved oncological outcome [3, 4, 38] although this observation requires prospective validation. Control of the blood pressure is essential to avoid cardiovascular toxicity including myocardial infarction, stroke, heart failure, reversible posterior leukoencephalopathy, proteinuria and renal failure. A reasonable approach is to use an angiotensin converting enzyme [14, 23, 36] inhibitor or an angiotensin receptor blocking [7, 23, 41] agent first, and after maximal dose with such an agent, add a beta blocker or a calcium channel blocker. It is important to mention that certain calcium channel blockers, such as diltiazem and verapamil, should be avoided for concern regarding a potential interaction with TKIs and inhibition of their anti-tumor activity. Some patients may require 3 anti-hypertensive agents for adequate control of their blood pressure. We recommend switching to a different class of antihypertensive agents, and potentially decreasing the number of agents used to control hypertension, if the patient's blood pressure is not controlled with 3 antihypertensive medications.

One of the most serious adverse events associated with the anti-VEGF TKIs is cardiac toxicity, including MI and/or decreased ejection fraction [2, 5-8, 12, 13, 15-17, 20, 22, 23, 25, 27, 29, 31, 32, 35-40, 42]. Cardiac toxicity has been observed and reported more commonly with sunitinib[12][8, 29]but can also occur with sorafenib and pazopanib. The incidence of cardiac toxicity is a matter of debate. The phase III study evaluating frontline treatment of renal cell carcinoma patients reported an incidence of grade three or higher cardiac toxicity below ten percent.[9, 23, 35] A smaller study specifically evaluating cardiotoxicity in patients treated for renal cell carcinoma and gastrointestinal stromal tumors, reported that nearly 30% of patients treated with sunitinib experienced a drop of EF by echocardiography or myocardial uptake gated assessment (MUGA) scanning, but less than 10% of patients receiving the drug for an extended duration required discontinuation of therapy because of decreased EF. [8] Performing baseline and follow up cardiac contractility assessment is important, in particular on patients with high-risk features which include prior cardiac events and diabetes. A high index of suspicion for the development of heart failure in patients who demonstrate symptoms of fatigue and increasing shortness of breath is essential. Management of TKI induced heart dysfunction usually requires cessation of systemic therapy for a period of time, which may have serious consequences for oncological outcomes. Patients may benefit from ACE inhibitors and beta blockers, and the majority of them improve with return of EF to baseline following medical therapy and discontinuation of the TKI. Switching to an alternative agent other than a TKI is a potential solution, while

awaiting recovery of cardiac function. Once EF has reached a reasonable level, rechallenge with a non-sunitinib TKI can be contemplated, with scrupulous cardiac follow up.

The management of significant proteinuria [9] is challenging, since there is no known effective treatment for it, other than interruption of therapy. Proteinuria is usually reversible after interruption of the TKI, but in some patients, it may take several weeks, even months, before it returns to an acceptable level (less than 1 gm/24 hours). The recently described random urine protein over creatinine (UPC) ratio)[9] is now widely used to monitor proteinuria and offers convenience while maintaining a high degree of concordance with 24-hour urine collections. We would withhold the TKI, if UPC is >2. Patients at risk for developing significant proteinuria are those with diabetes mellitus, hypertension, renal disease and prior exposure to anti-vascular endothelial growth factor [6] therapy, which includes the TKIs and bevacizumab. In our experience, patients who develop nephrotic syndrome secondary to anti-VEGF therapy continue to be at risk for developing this toxicity later if treated with mammalian target of rapamycin (mTOR) inhibitors, even after UPC returns to <1 following discontinuation of the anti-VEGF agent.

All 3 TKIs produce fatigue, with pazopanib being the best tolerated and sunitinib the worst tolerated in this regard. In our experience, sunitinib is better tolerated when given on a 2-wk on, 1-wk off schedule, rather than the traditional 4-wk on, 2-wk off schedule. Retrospective data suggest improved compliance on this regimen. [3, 4] Obviously, prospective data are needed to formally validate scheduling changes in drug administration. Fatigue is best managed with good sleep hygiene and the incorporation of appropriate daily exercise.

Gastrointestinal toxicity including nausea, vomiting, stomatitis, bloating, diarrhea, reflux and dysgeusia occur more commonly with sunitinib and are least common with pazopanib. The mechanism of diarrhea associated with these TKIs is not well understood. Anti-diarrheal agents such as loperamide, diphenoxylate and atropine and occasionally tincture of opium may be used. Occasionally, agents that sequester bile acid, such as cholestyramine, may be helpful, if the diarrhea is not controlled with the other agents. Changing to an interrupted treatment schedule, with patient initiated breaks at the time of side-effect induced treatment intolerance may improve symptom control. Close coordination between the patient and the treatment team is necessary to achieve success with this approach.

Abnormal liver function tests (LFTS) including elevated alanine aminotransferase [13, 20, 25], aspartate transaminase [2, 4-6, 8, 10-12, 14-23, 25-43, 45, 46] and bilirubin have been reported with all 3 agents but are more common and serious with pazopanib.[13, 41] Careful monitoring of LFTs to avoid serious hepatotoxicity is mandatory in patients receiving pazopanib and is the main reason for discontinuation of therapy with this TKI due to toxicity.

The hand-foot skin reaction (HFSR) is characterized by painful blisters and/or calluses on the palms and soles, often accompanied by tingling and desquamation. HFSR is worst with sorafenib and least with pazopanib. Supportive treatment includes avoidance of hot water and early initiation of heavy emollients, in combination with the use of cotton gloves and/or socks and gel inserts for enhanced skin protection. Topical agents containing aloe vera, lidocaine, or clobetasol may also be helpful.

A side effect associated with sorafenib but not with sunitinib and pazopanib is the development of actinic keratosis and squamous cell carcinoma of the skin. This complication occurs in approximately 7% of patients treated with sorafenib.[2, 13] The mechanism of this complication is not clear but could be related to inhibition of the BRAF pathway, one of the targets of sorafenib but not sunitinib and pazopanib.

Impaired wound healing with occasional wound dehiscence may occur with the three TKIs, but not as commonly as with bevacizumab (see below). Bleeding[7, 10, 21, 25] and a hypercoagulable state leading to venous and arterial thrombosis[7, 21, 25] have been reported with these TKI, but are more commonly associated with the use of bevacizumab. A rare but serious complication is gastrointestinal perforation.

A number of patients receiving TKIs develop thyroid function tests abnormalities.[37, 42] This is observed more commonly with sunitinib,[37, 42] may contribute to fatigue in these patients, and often require treatment with thyroid supplementation. Correction of TSH does not necessarily abrogate the fatigue, suggesting that fatigue is multifactorial. Conversely, patients with normal range thyroid stimulating hormone (TSH) and low- normal free T4 index levels may benefit from low-level levothyroxine supplementation. Referral to an endocrinologist may help optimize the management of thyroid dysfunction in these individuals.

Anti-VEGF antibody [14, 15, 27, 39]—Bevacizumab is the best tolerated of all FDA approved agents for mRCC, with virtually none of the gastrointestinal toxicity that is commonly seen with the anti-VEGF TKIs such as nausea, vomiting, diarrhea, bloating, abdominal pain, anorexia, stomatitis, but it can rarely lead to GI perforation similar to the TKIs.

The most common adverse events associated with bevacizumab are hypertension, proteinuria, renal insufficiency and bleeding.[14-16, 39, 42, 43] In mRCC, bleeding secondary to bevacizumab is minor especially if the patient is not on anticoagulation, but caution needs to be exercised if the patient has involvement of the tracheobronchial tree with mRCC. Bevacizumab should not be administered in case of any bleeding due to tumor involvement until the bleeding is stopped with local therapies such as embolization, surgery or radiation. The most common adverse event leading to discontinuation of bevacizumab in mRCC patients is nephrotic syndrome and renal insufficiency. Hypertension is usually manageable using a similar algorithm as in patients treated with anti-VEGF TKIs.

Mammalian target of rapamycin analogs (temsirolimus, everolimus)—The two mTOR inhibitors, temsirolimus and everolimus, carry a slightly different side-effect profile that includes metabolic syndrome and non-infectious pneumonitis. [23, 36]Monitoring of the fasting glucose concentration is thus recommended for patients receiving these 2 mTOR inhibitors; dietary modification and initiation of oral hypoglycemic agents are effective initial management strategies. Total cholesterol and triglyceride concentrations should also be monitored, with lipid-lowering medications being started when appropriate. The stomatitis associated with temsirolimus and everolimus is relatively mild and can be managed with good oral hygiene and pain control. [5]

Drug related pneumonitis was reported in less than 10% of mRCC patients treated on the temsirolimus phase 3 trial [23] and in 14% of patients treated on the everolimus phase 3 trial.[36] However, subsequent reports from the phase 3 trials with these 2 mTOR inhibitors and our experience with these agents in practice indicates a much higher incidence approaching 40 %. Additionally, some patients have developed a symptomatic decrease in pulmonary ventilation perfusion capacity (DLCO) without obvious radiographic changes. Although not prospectively validated, the management of pneumonitis requires close follow up and no dose reduction or withholding if radiographically mild and the patient is asymptomatic. If the patient is symptomatic, or the radiographic changes are substantial, stopping therapy is advised, and patients also may benefit from a short course of systemic corticosteroids. Care must be exercised in administering steroids to patients on mTOR inhibitors, as these agents are potentially immunosuppressive. Once radiographic findings or

symptoms have improved, a rechallenge with mTOR inhibitor at a reduced dose can be attempted.

Expert Commentary

We are seeing a slow increase in the incidence of long-term survivors with mRCC. Optimizing surgical management of the primary tumor, judiciously selecting individuals for metastasectomy, and paying careful attention to the side effects associated with targeted therapy administration will improve the quality of life and potentially the survival of these individuals even more.

A few specific points should be reiterated. First, cytoreductive nephrectomy is still a standard in patients who receive molecularly targeted agents, but should be reserved for individuals who have a good performance status, a resectable primary tumor, and do not have extensive or threatening systemic disease. Second, choice of systemic therapy is based on tumor histology and risk strata, but close attention needs to be paid to the patient's specific comorbidities to achieve a good match between therapy and the individual. Third, paying close attention to toxicities will pay long term dividends in the form of decreased fatigue, end-organ damage, and overall quality of life.

Five Year View

As systemic therapy, biomarkers of response, and surgical and minimally invasive techniques improve, we will see a further emphasis on the need to balance the benefits and shortcomings of molecularly targeted therapies in patients with mRCC. In the next five years, we will see improvements in the potency of anti-VEGF therapies and drugs the block the mTOR related signaling events. These improvements will permit further development of the presurgical paradigm, which will result in a higher percentage of nephron sparing procedures. Improvements in genomic, transcriptomic, proteomic, seromic and imaging tools will allow us to predict which patients are likely to respond to a particular agent. We will see improvements in minimally invasive and organ sparing interventional approaches. In aggregate, these changes will further move metastatic RCC towards becoming a chronic disease for most patients, and will increase the cure fraction.

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Key issues

1. For good prognosis patients with a resectable primary tumor, cytoreductive nephrectomy is a current standard of care.
2. Attempts at performing nephron sparing surgery should be made.
3. A good understanding of the particular side effect profiles of available agents will permit matching of drug to patient comorbidities.
4. Careful side effect management will greatly improve compliance, quality of life, and ultimate oncologic efficacy of systemic therapy,
5. Metastasectomy can be considered in patients with oligometastatic disease, and may result in prolonged disease free survival.
6. For patients who are rendered free of disease on molecularly targeted therapy, discontinuation of therapy and careful observation has been shown to be safe in retrospective series.

Table 1

Presurgical and Neoadjuvant Studies using Molecularly Targeted Agents.

Group	N	Study Type	Treatment	Primary Tumor	Downstaging?	Metastases?
MD Anderson Cancer Center[11, 13, 27]	50	Prospective	Bevacizumab+/-Erlotinib	Resectable	0/50	All Patients
University of North Carolina[10]	30	Prospective	Sorafenib	Resectable	Not Determined	Some Patients
MD Anderson Cancer Center[32]	44	Retrospective	Sunitinib Sorafenib Bevacizumab	Resectable	Not Determined	Some Patients
Cleveland Clinic[2, 43]	19	Retrospective	Sunitinib Sorafenib Bevacizumab	Unresectable	2/19	Some Patients
VU University Medical Center[46]	17	Retrospective	Sunitinib	Mixed	4/17 patients underwent nephrectomy	Some Patients
UCLA[40]	4	Case Series	Sunitinib	Mixed	4/4	Some Patients