Integration of Surgery and Systemic Therapy in the Treatment of Locally Advanced and Metastatic Renal Cell Carcinoma

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Prior to 2006, the integration of surgery and systemic therapy in the management of locally advanced and metastatic renal cell carcinoma was fairly straightforward. In the locally advanced setting, there was no known effective adjuvant therapy available, such that aggressive surgical resection followed by risk-stratified surveillance was the standard of care. In the metastatic setting, level one evidence—in the context of immunotherapy with interferon—promoted upfront cytoreductive nephrectomy in properly selected patients, followed by the adjuvant administration of immunotherapy. This practice was based on two randomized studies comparing immunotherapy with and without prior cytoreductive nephrectomy, which showed prolonged survival for operated patients and the realization that the primary tumor rarely, if ever, responded to systemic immunotherapy.[1,2]

We have now entered a new era in systemic therapy for renal cell carcinoma, where, based on a further understanding of the biology of renal cell carcinogenesis and progression, novel therapies that target both tyrosine receptor kinases as well as the mTOR pathway have been developed and implemented in the clinic. As a consequence, we are now seeing unprecedented tumor response rates, with resultant dramatic improvements in progression-free and overall survival for patients. In concert with these developments, some have questioned both the need for, as well as the proper integration of, surgery with these new "targeted" systemic therapies in the treatment of both locally advanced and metastatic disease. Ongoing clinical trials in both the locally advanced and metastatic setting are examining the role of tyrosine kinase inhibition as an effective adjuvant strategy, as well as its proper integration with surgery in the setting of metastatic disease. In addition, the concept of neoadjuvant or presurgical therapy is being tested through the clinical trials mechanism. As we await the results of these important clinical studies—which, in most cases, will be many years in the future—the practicing clinician is left with little, if any, high-quality data to guide the management of patients with locally advanced and metastatic disease.

A logical progression in the development of targeted systemic therapy that has proved effective in the treatment of metastatic disease is the application of these agents in the adjuvant setting, following surgery for renal cell carcinoma at high risk of relapse. But as we have learned from the history of adjuvant therapy development, activity in the metastatic setting does not necessarily translate to efficacy in the adjuvant setting at a time of minimal residual disease burden. In fact, to date, it never has.[3] The adjuvant therapy clinical trials landscape is littered with negative trials involving agents that demonstrated some modicum of efficacy in the metastatic setting, such as immunotherapy, vaccines, hormones, and even some antiangiogenic approaches. Why are we to believe that these new targeted therapies will be different? In fact, some have questioned the logic of using these agents in the adjuvant setting, as their main mechanism of action appears to be antiangiogenic rather than antitumoral, such that they may prolong time to disease recurrence but be ineffective in actually eliminating micrometastatic disease. Nonetheless, there are several ongoing clinical trials, such as the Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE) trial, the Sunitinib Treatment of Renal Adjuvant Cancer (S-TRAC) trial, and the Phase III Randomized Double-blind Study Comparing Sorafenib with Placebo in Patients with Resected Primary Renal Cell Carcinoma at High or Intermediate Risk of Relapse (SORCE) trial, all of which are examining the role of tyrosine kinase inhibition with either sunitinib or sorafenib in the adjuvant setting. In addition, another clinical trial with pazopanib began accruing patients at the end of 2010. Early reports indicate that toxicity from these agents may be a significant problem in ensuring compliance with therapy, although indications of efficacy will not be realized for many years to come.

Another novel therapeutic paradigm that has demonstrated efficacy in the setting of other advanced malignancies, such as bladder, colorectal, and lung cancer, is the concept of neoadjuvant or presurgical therapy, and is being applied in the setting of locally advanced and metastatic renal cell carcinoma. As outlined in Table 1, there are several potential advantages and disadvantages to this treatment approach that require further investigation. However, the main impetus for the implementation of this strategy has been the hope for primary tumor downstaging/downsizing, which could decrease surgical morbidity and increase the utilization of nephron sparing, as well as using antitumoral response as a selection criteria for the implementation of cytoreductive surgery. The literature is replete with anecdotal evidence of primary tumor responses to sys-

Table 1. Risks and Benefits of Neoadjuvant (Presurgical) Therapy for Renal Cell Carcinoma

Benefits	Risks
• Primary tumor downstaging/sizing – Decreased surgical morbidity – Increased utilization of nephron sparing – The "unresectable" become "resectable" – Improved prognosis	• May increase surgical morbidity – Wound healing – Local tumor progression
• Eliminate/downsize metastatic tumor burden	• Disease may progress (locally or metastatic) on therapy
• Operate on "responding" patients (litmus test)	• Therapy may alter biology of metastatic disease adversely

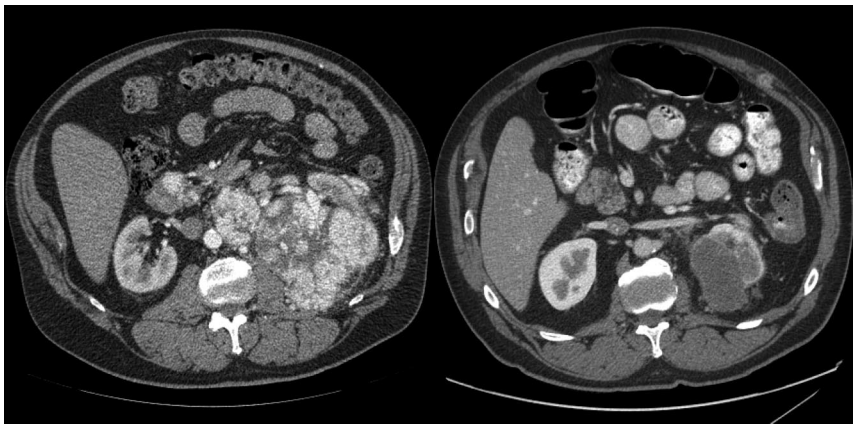

Fig. 1. Effect of presurgical sunitinib therapy. Patient received two courses of sunitinib and went on to laparoscopic cytoreductive nephrectomy following tumor response.

temic targeted therapy, with dramatic reductions in primary tumor volume, regression of venous tumor thrombi, and increased utilization of nephron-sparing surgery, such that many have hypothesized that neoadjuvant approaches may be the future standard in the management of patients with unresectable or borderline resectable disease.[4] Indeed, as shown in Fig. 1, dramatic regression of both the primary tumor and nodal metastases can be realized with presurgical or neoadjuvant approaches, such as seen in this patient treated with sunitinib at M. D. Anderson Cancer Center, but it remains to be seen if these types of responses are reliable, predictable, and do result in improved patient outcomes.

We recently published our retrospective experience examining primary tumor response to neoadjuvant or presurgical therapy in a cohort of more than 160 patients at M. D. Anderson Cancer Center.[5] In keeping with other published literature on the topic, our group found that dramatic changes in the primary tumor—as a consequence of neoadjuvant or presurgical therapy—were the exception rather than the rule. Most patients demonstrated little, if any, response in either their primary tumor or venous thrombus when present. In fact, just as there were some patients with impressive tumor regressions as a consequence of therapy, there were a significant number of patients who had dramatic progression of their tumor on therapy. Does this mean that these neoadjuvant or presurgical strategies should be abandoned? Although reliable responses in the primary tumor may not be realized with the current generation of systemic targeted therapies, there is arguably a potential benefit of this approach that transcends the need for primary tumor response. Patients who progress on therapy could be spared a highly morbid surgical intervention from which they are unlikely to benefit, such that response to targeted therapy could be used as a selection criteria or "litmus test" to identify those patients most likely to benefit from the integration of surgery with systemic targeted therapy in the management of their disease.

In conclusion, the most appropriate integration of surgery with systemic targeted therapy remains yet to be defined in the setting of locally advanced or metastatic renal cell carcinoma. Ongoing clinical trials will hopefully clarify treatment paradigms with level one evidence as to the most appropriate approach. Although some question the continued need for surgical therapy, in light of the impressive responses seen with these agents, the lack of reliable or complete responses and the inevitable development of therapeutic resistance would indicate that surgery will remain an important part of the treatment paradigm in both locally advanced and metastatic disease.

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