Multimodal Approaches in the Management of Locally Advanced and Metastatic Renal Cell Carcinoma: Combining Surgery and Systemic Therapies to Improve Patient Outcome
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Abstract
Patients with locally advanced renal cell carcinoma are at high risk of metastatic relapse following surgery. Patients with metastatic disease have a poor prognosis and few systemic therapy options. Radiation, chemotherapy, hormonal therapy, vaccines, and immunotherapy have all been tested as adjuvant therapy without benefit. Neoadjuvant therapy in the metastatic setting holds promise as a new treatment paradigm. It can serve as a litmus test to allow proper patient selection for aggressive surgical intervention and may provide limited downstaging of primary tumors in selected cases. It can also provide a histologic assessment of the effect of targeted therapy. Application of this paradigm may have merit in the locally advanced setting as well. Effective adjuvant therapy for renal cell carcinoma remains elusive. The benefit of new targeted therapies has yet to be tested in this setting. Neoadjuvant strategies that integrate aggressive surgical intervention with systemic therapy may hold promise as a treatment paradigm.

Development of an Effective Adjuvant Strategy for Locally Advanced Renal Cell Carcinoma at High Risk of Relapse following Surgery

Renal cell carcinoma remains one of the most lethal of urologic malignancies despite recent inroads into the biology of progression and metastases that have translated into the development of novel therapies. Despite this, effective adjuvant therapy for patients with renal cell carcinoma at high risk of relapse following surgery remains elusive in 2006. The ideal adjuvant is nontoxic, is administrable in the outpatient setting, has shown activity in metastatic disease, has demonstrable efficacy against the standard of care (observation) in phase 3 randomized trials, and can be applied in patient populations most likely to benefit from adjuvant therapy, those with high-risk disease.

Defining Risk of Recurrence

Despite an increase in early detection, ~30% of patients who present with localized kidney cancer develop metastases during the natural history of their disease (1). Advanced pathologic stage is recognized as an adverse prognostic factor in patient outcome. The presence of extracapsular extension, venous involvement, or nodal metastases is associated with an increased risk of an adverse clinical outcome (2, 3). In addition to stage, several nomograms now exist that include additional clinical and pathologic variables to improve the categorization of patients with regard to risk of recurrence. These include the addition of grade and Eastern Cooperative Oncology Group performance status (University of California at Los Angeles Integrated Staging System), tumor size and the presence or absence of histologic tumor necrosis (Mayo Clinic Stage, Size, Grade, and Necrosis Score), and histology and symptoms at presentation (Memorial Sloan-Kettering Cancer Center Nomogram), among other clinical features (4–8). These nomograms stratify patients according to risk of recurrence, some with external validation, to precisely identify those at highest risk and therefore most in need of an adjuvant therapy. Furthermore, these risk paradigms can be used to develop risk-stratified surveillance protocols for postoperative follow-up. Research in prognostic markers for renal cell carcinoma is now focused on correlating tissue and serum molecular markers with outcome to further define and refine risk assessment paradigms (9).

Adjuvant Therapy for Renal Cell Carcinoma: Where Have We Been?

Many adjuvant strategies have been tested during the last several decades. Initial studies focused on improving local control through the application of radiation therapy in the adjuvant or neoadjuvant setting. Radiation has not proved to be an effective adjuvant for several reasons. First and foremost, renal cell carcinoma is largely a radioresistant tumor. Further, local failure is uncommon following radical nephrectomy. Recurrent disease typically is metastatic, developing at sites remote from the primary tumor. In randomized, prospective trials, radiation therapy has failed to show an improvement in
prognosis and is largely relegated to the palliative treatment of symptomatic bone and central nervous system metastases (10–12).

With the knowledge that renal cell carcinoma cells possessed hormonal receptors, hormonal therapy with medroxyprogesterone acetate has been used in the metastatic setting, with a response rate of 5%. Pizzocaro et al. (13) conducted a multicenter adjuvant trial with this agent, where patients were randomized to receive medroxyprogesterone acetate versus observation. No benefit with regard to recurrence-free survival was noted in the treatment group, and significant toxic effects associated with the agent were reported.

Renal cell carcinoma has been a disease where immunotherapeutic strategies have been developed, tested, and used in the metastatic setting. From early descriptions of spontaneous regression of metastatic foci following resection of the primary tumor to the pathologic finding of tumor-infiltrating immune cells in nephrectomy specimens, renal cell carcinoma and immune dysfunction have been linked, with treatment strategies designed to augment immune function in the host to attack the tumor (14, 15). These strategies have included immunotherapy, with interleukin-2 and/or IFN alfa, vaccine strategies, dendritic cell therapies, and even allogeneic bone marrow transplantation (16–18). All of these treatment paradigms share the common recognition that there is immune dysfunction in patients with renal cell carcinoma and that modulation or stimulation of the immune system may overcome the dysfunction and improve patient outcome.

The activity of interleukin-2 and IFN, alone and in combination, has been well documented in the metastatic setting. Response rates in the range of 15% to 20% have been noted, with a durable complete response of 5% for interleukin-2 (16). Until recently, immunotherapy with these agents remained the standard of care for patients with metastatic renal cell carcinoma, and logically, efforts ensued to test the efficacy of these agents in the adjuvant setting. Multiple randomized phase 3 trials have been done to examine the efficacy of IFN, IFN in combination with vinblastine, and interleukin-2. None of these trials have shown a benefit for treated patients when compared with observation with regard to improvements in disease-free or overall survival (19–27).

Despite the lack of efficacy noted with cytokines in the adjuvant setting, targeting the immune system as a therapeutic intervention continues to intrigue clinicians. Reports of improved survival associated with primary tumor embolization before nephrectomy in locally advanced disease, as well as spontaneous regression of metastatic foci in concert with radiofrequency ablation of the primary tumor, suggest that immunomodulation through unique tumor antigen presentation may improve outcomes in this disease (28, 29).

Patient-derived tumor vaccines have been used in the treatment of renal cell carcinoma, both in the metastatic setting and, more recently, as adjuvant therapy in locally advanced disease. In this strategy, tumor cells, derived from nephrectomy specimens, are processed to provide unique tumor antigen presentation in the attempt to stimulate the host immune system to target residual cancer foci. Galligioni et al. (30) reported on the use of a vaccination strategy with irradiated tumor cells injected with an adjuvant and noted no significant improvement in disease-free survival for the treatment group when compared with observation. More recently, a phase 3 randomized trial from Germany was reported, where patients with high-risk locally advanced renal cell carcinoma were randomized to observation versus a tumor lysate formulation (31, 32). Initial reports suggested a significant benefit with regard to progression-free survival for the vaccination arm in the trial ($P = 0.0204$), particularly in patients with $T_2$ disease ($P = 0.039$); however, critics of this study argue that a significant percentage of patients in the vaccine arm never got their vaccine and therefore were not included in the analysis and that this study would lose its significance in a true intent-to-treat analysis.

The results of the largest randomized phase 3 adjuvant trial in renal cell carcinoma were recently reported through a press release by Antigenics, Inc. This trial centered on the use of a tumor-derived vaccine preparation that involved the isolation of heat shock protein 96 from a patient's tumor harvested at nephrectomy. Heat shock proteins are peptide chaperones in the cell that bind to specific cell surface receptors and can elicit both cellular and humoral immune responses. By focusing on the isolation of heat shock proteins in the vaccine preparation, a highly purified peptide library representing cellular antigens (both tumor derived and normal) can be isolated, which is the technology behind vitespen (Oncophage). In this trial, 818 patients with locally advanced disease (the spectrum of inclusion criteria ranged from $T_3$, high-grade to node-positive disease) were randomized to receive vaccine versus observation. The trial was designed to show an improvement in disease-free survival for patients receiving vaccine from 60% to 75% (32). The trial recently underwent an interim analysis after data lock that failed to show a significant difference between the observation arm and the vaccine arm with regard to disease-free or overall survival (33). Of note, there were a significant number of patients included in the trial who actually had residual disease at baseline and many others who were lost to follow-up. As a consequence, the number of required events the trial was powered for was significantly less than anticipated. Further data analysis and follow-up of patients are ongoing, and the final estimation of the benefit of this vaccine preparation remains in question at present.

The antiangiogenic, immunomodulatory drug thalidomide has been applied in the adjuvant setting. At the M. D. Anderson Cancer Center (Houston, TX), thalidomide was used as a single agent in the metastatic setting, with a partial response rate of 10.5% and a significant number of patients with stable disease while undergoing therapy (34). As a consequence, thalidomide was tested in the adjuvant setting in a single institution randomized phase 3 trial (thalidomide, 300 mg daily for 2 years, versus observation) that is ongoing currently. In a recent interim analysis, with 46 patients randomized, there was no difference between the two groups with regard to disease-free survival ($P = 0.945$), but the group receiving thalidomide had a significantly better disease-specific survival when compared with observation ($P = 0.048$). Of note, significant dose reductions and early termination of therapy have been seen in the thalidomide arm of the trial due to toxicity.

There currently are two ongoing adjuvant trials for patients at high risk of relapse following nephrectomy. The Rencarex Trial is a multicenter phase 3 trial testing the WX-G250 antibody...
against carbonic anhydrase IX versus placebo in the adjuvant setting. This trial has been open for several years, suffered early from accrual problems, and was recently revised to improve its accrual rate (35). E2805 (ASSIURE) was activated in April 2006 and is opening at selected sites throughout the country through intergroup mechanisms. This trial, proposed by the Eastern Oncology Cooperative Group, is a three-arm trial that will randomize 1,332 patients to 54 weeks of sorafenib, sunitinib, or placebo following nephrectomy (Fig. 1). All histologic types will be included, and the trial design is such that it has an 80% power to detect a 33% improvement in disease-free survival (35).

In summary, there is no proven effective adjuvant therapy for patients with renal cell carcinoma at high risk of relapse following nephrectomy. There are many novel therapies showing efficacy in the metastatic setting that are being brought forward into the adjuvant setting for testing that hold much promise. Issues of toxicity, problems with patient accrual, and the conduct of multiple competing trials for the same patient population remain real challenges that must be faced and dealt with if we are to advance the field.

One other consideration in the locally advanced renal cell carcinoma setting is the concept of neoadjuvant therapy before surgical extirpation. There have been some nonrandomized, retrospective studies that have examined the role of preoperative tumor embolization as a neoadjuvant “therapy” before radical nephrectomy that have suggested a benefit for the embolization, but these findings await prospective validation (28, 36). The benefit of embolization is hypothesized to be the release of tumor antigens as a consequence of the embolization, with resultant immunologic effects. The concept of applying systemic therapy before surgery for some defined time period remains controversial. Such a paradigm would allow an assessment of resected tissue for treatment effect and also potentially translate into an improvement in disease-free and overall survival as a consequence of the systemic therapy given before surgery. Critics of this approach argue that the systemic therapy may translate into increased morbidity in the perioperative period and that the delivery of neoadjuvant therapy before surgery would result in an unacceptable delay in the implementation of what would otherwise be a potentially curative surgical procedure for what remains an undefined benefit.

Adjuvant Therapy for Locally Advanced Renal Cell Carcinoma: E2805

- Locally Advanced RCC
  1. T2NOM0 Grade 3-4
  2. T3NOM0
  3. T4NOM0
  4. TanyN1-2MB

- Pathology confirmed
- 1332 patients (444 arm)
- 80% power to detect 33% improvement in RFS

Fig. 1. Schema for Eastern Cooperative Oncology Group 2805 randomized phase 3 adjuvant trial comparing 1 yr of sorafenib or 1 yr of sunitinib with placebo in patients with locally advanced renal cell carcinoma at high risk of relapse following surgery.

In 2001, the results of two randomized trials examining the role of cytoreductive surgery in conjunction with immunotherapy (IFN alfa) were reported. In the two prospective trials, as well as in a combined meta-analysis, the survival of patients who underwent cytoreductive nephrectomy before IFN was significantly better than those treated with systemic IFN therapy alone (39–41). Interestingly, responses to systemic therapy were poor regardless of whether surgery was incorporated into the treatment plan and that, with more effective systemic therapy, further benefits from cytoreductive surgery before systemic therapy might be realized (42).

The risks associated with this treatment approach include disease progression during recovery from surgery and surgery-related morbidity or mortality, which would preclude patients from receiving any systemic therapy (38). Although these complications are rare with proper patient selection, it still should give one pause in the consideration of doing cytoreductive surgery, particularly in the setting of a locally advanced primary tumor.

Although cytoreductive surgery followed by systemic therapy has largely become a standard treatment paradigm in this disease, some debate as to the best timing of nephrectomy still remains. It is widely held that nephrectomy is an important part of the multidisciplinary treatment approach; it is not at all clear that upfront surgery followed by systemic therapy is the best treatment model. It is possible that delaying nephrectomy while assessing the response to a defined course of systemic therapy might be realized (42).
therapy may represent a reasonable treatment approach in the setting of metastatic renal cell carcinoma.

Neoadjuvant therapy is not a new concept. As stated earlier, in the past, nephrectomy was only done for palliation or in the rare patient who responded to therapy. What is new is the development of more effective systemic therapies, which have provided significant improvements in time to progression and survival that were unimaginable with immunotherapeutic approaches, even as second-line therapy after immunotherapy failures (17). As a consequence, neoadjuvant paradigms remain a treatment strategy worth revisiting.

The most significant benefit of the neoadjuvant approach in the treatment of metastatic renal cell carcinoma is that it can serve as a litmus test to select patients who are responding to therapy and most likely to derive benefit from the proposed surgery. Patients progressing with therapy would not be subjected to the morbidity and potential for mortality of a surgical endeavor that they are unlikely to derive any significant benefit from. Furthermore, neoadjuvant approaches can provide tissue to study the biology of renal cell carcinoma progression and metastasis as well as the mechanism of action of targeted therapies directed at the tumor. Finally, neoadjuvant therapy before cytoreductive surgery may provide some downstaging of the primary tumor that may facilitate surgical extirpation. Although primarily anecdotal at present, there does seem to be activity of the newer targeted therapies, such as the tyrosine kinase inhibitors, at the level of the primary tumor that may cause downstaging.2

Arguments against the neoadjuvant approach include the fact that it is unproven when compared with the survival benefit shown with upfront cytoreductive nephrectomy in randomized trials. Further, there is the real risk of increased surgical morbidity and postoperative complications associated with the use of systemic therapy before surgery. A historical analogy pertinent in this comparison is retroperitoneal lymph node dissection for metastatic testicular cancer, where the use of chemotherapy before surgery increases the difficulty of the operation and the risk of intraoperative or postoperative complications by several orders of magnitude.

We have embarked on several neoadjuvant protocols for conventional (clear cell) metastatic renal cell carcinoma at M. D. Anderson Cancer Center that are currently ongoing and accruing patients. The treatment algorithms are depicted in Fig. 2A to C. Targeted therapies chosen for these approaches include bevacizumab with erlotinib, sorafenib, and sunitinib in separate phase 2 trials. Initial observations would suggest that it is feasible without untoward intraoperative or postoperative complications, and we have, in fact, seen responses in some but not all of the primary tumors thus far treated. The true results of these endeavors await further patient accrual and follow-up.

**Conclusions**

In 2006, the standard of care for locally advanced renal cell carcinoma remains observation following surgical resection. Ongoing trials with investigational agents that target tumor-specific molecular pathways in the adjuvant setting await further accrual and follow-up. Cytoreductive nephrectomy

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2 E. Jonasch, personal communication.

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**Fig. 2.** A, schema for neoadjuvant phase 2 trial with bevacizumab and erlotinib in patients with metastatic clear cell carcinoma and primary tumor in place. B, schema for neoadjuvant phase 2 trial with sorafenib in patients with metastatic clear cell carcinoma and primary tumor in place. C, schema for neoadjuvant phase 2 trial with sunitinib in patients with metastatic clear cell carcinoma and primary tumor in place.

remains an integral part of the management of metastatic renal cell carcinoma; however, the best integration of systemic therapy with surgery remains in question. Neoadjuvant therapy in the setting of metastatic renal cell carcinoma, as a new treatment paradigm, may serve as a litmus test to allow more selective application of surgery to only those patients who will derive the most benefit.

**Open Discussion**

Dr. Atkins: Is progression-free survival going to be a clinically meaningful end point for adjuvant therapy protocols
when these patients will likely receive the same agents after they
progress? Is it really likely that we are going to eliminate the last
cell with these therapies?

Dr. Wood: Based on history, the answer to that question is
no.

Dr. Kwon: Do you have any remedies for how to make these
studies less cumbersome?

Dr. Fliglin: I think that the trials would be less cumbersome if we
used other systems for prognosis, such as those that require
consistent protein expression profiles that identify high-
risk groups different than the clinical paradigms of grade,
performance status, and TNM. Are we really ready to ask these
big questions based on only clinical selection criteria when it
may be that molecular and protein expression criteria are just
around the corner?

Dr. Wood: Obviously, molecular characterization of these
patients and molecular surrogate end points that could be used
to identify response to therapy would be tremendously helpful
and decrease the size and cumbersomeness of these trials, but
currently those things do not exist.

Dr. Kwon: There is a real opportunity to start implementing
some of these prognostic algorithms, whether it be UCLA’s or
Mayo’s, or to combine and streamline these algorithms.

Dr. Libermann: Apparently, none of these types of mono-
therapy do much. Is it still valid to do these kinds of clinical
trials with monotherapy or do we have to rethink how we can
combine multiple drugs in the clinical trials because maybe
none of them will have an effect by themselves but a
combination of them might be more effective, and we might
be able to reduce the dose for each individual drug to a less
toxic dose?

Dr. Wood: Potentially, that’s true, but with combinatorial
therapy you also potentially increase the toxicity without
necessarily increasing the efficacy of the drug. It is important
to identify which drugs are effective as monotherapy before you
start using combinatorial therapy because you may be
increasing the toxicity without increasing the effect.

Dr. Rini: It’s not fair to say that these drugs do not do much
as monotherapy. Sunitinib, sorafenib, and bevacizumab all
shink tumors in about 70% of patients, which is infinitely
greater than anything we have ever had.

Dr. Flaherty: Certainly, some patients have had remarkable
courses with these agents.

Dr. Atkins: These are active agents in phase 3 trials. Even
though they may not be curbing people, most patients are
clearly getting clinical benefit and progression-free survival is
certainly prolonged. Therefore, these are good agents to test
in the adjuvant setting. The question is are we ready to do
these studies and will these agents work in the adjuvant
setting.

Dr. Flaherty: The toxicity point is critical because if
combination therapies are going to add toxicity, then these
regimens are borderline in terms of their tolerability for the
adjuvant setting.

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