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Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma: Is It Still Imperative in the Era of Targeted Therapy?

Allan J. Pantuck, Arie S. Belldegrun, and Robert A. Figlin

Abstract In the era before cytokine therapy, controversy existed about the need for cytoreductive nephrectomy in treating patients with metastatic renal cell carcinoma. In 1978, Dekernion showed that nephrectomy alone had no effect on survival. During this period, removal of the malignant kidney was confined to palliative therapy in some settings of metastatic RCC, such as pain related to the kidney mass, intractable hematuria, erythrocytosis, uncontrolled hypertension, or poorly controlled hypercalcemia. When interleukin-2 was approved by the Food and Drug Administration in 1992, the role of nephrectomy was reexamined. After a decade of controversy, two randomized controlled studies established that cytoreductive surgery has a role in properly selected patients and offers a survival advantage when done before cytokine therapy. Unfortunately, the mechanisms underlying this benefit remain poorly understood. Immunotherapy may work best when there is a small volume of cancer present, and removing a large primary tumor may prevent the seeding of additional metastases. Data have also suggested that primary tumors were capable of producing immunosuppressive compounds that might decrease the efficacy of immunotherapy. Another hypothesis suggested that removing the kidney altered the acid/base status of the patient to such an extent that the growth of the tumor was hindered. With the emergence in 2006 of two targeted agents for advanced renal cell carcinoma, the role of cytoreductive nephrectomy has reemerged as a source of controversy. Although evidence-based medical practice suggests a role for nephrectomy before the use of targeted agents, the arguments for and against this practice will be weighed.

More than 200,000 new cases of kidney cancer are diagnosed annually and more than 100,000 deaths occur from this disease each year worldwide, with the highest incidence in North America, Europe, and Australia (1). Renal cell carcinoma (RCC) accounts for 3% of all adult malignancies and is steadily increasing at a rate of ~2.5% per year across population groups (2). Kidney cancer is the most lethal of the urologic malignancies with more than 40% of patients dying of their cancer (3). Approximately 20% to 30% of patients present with metastatic disease and 20% to 40% of patients undergoing nephrectomy for clinically localized RCC will develop metastases (4). Although it has been more than 35 years since the radical nephrectomy was standardized by the work of Robson and colleagues (5), the management of both localized and metastatic RCC has changed dramatically in the last 20 years, predicated on major advancements in renal imaging, surgical techniques, and the development of effective therapies for advanced disease, which have resulted in improved survival of a select group of patients and an overall change in the natural history of the disease (6).

Patients with metastatic RCC face a poor prognosis, with a historical median survival of 6 to 10 months and a 2-year survival of 10% to 20% (7); however, subsets of patients with advanced disease have shown improvements in survival. This improved outlook for some patients with advanced and metastatic RCC through the 1990s and up to the present time are related to the introduction of immunotherapeutic approaches and a better understanding of the role and timing of cytoreductive nephrectomy (8–10). In 1978, Dekernion et al. (11) showed that nephrectomy alone had a minimal effect on survival in patients with metastatic RCC, a widely held position in the era before the emergence of treatment with biological response modifiers.

The Era of Cytokine Therapy

Historically, the principle behind cytoreductive nephrectomy as a treatment for metastatic RCC was based on the immunologic phenomenon of "spontaneous" regression of metastasis after nephrectomy. However, in a review of 474

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patients with metastatic disease who underwent nephrectomy alone, only 4 (0.8%) experienced spontaneous regression of their metastatic disease (12). More recently, Marcus et al. (13) reported that of 91 patients, 4 (4.4%) with lung metastases only had complete regression of all metastatic disease after nephrectomy. Widely accepted historical indications for nephrectomy for metastatic RCC have been to improve quality of life. Removal of the malignant kidney may be of palliative benefit in some settings of metastatic RCC and is appropriate when the patient is having pain related to the kidney mass, intractable hematuria, erythrocytosis, uncontrolled hypertension, or persistent hypercalcemia that does not respond to pharmacologic agents (14). Surgery may also be directed at metastases to control local symptoms, which include the relief of spinal cord compression and fixation of fractures. Although nephrectomy alone for metastatic RCC was widely discredited, with the emergence of modern immunotherapy in the 1980s and 1990s, the role of nephrectomy and the relative efficacy of initial biological response modifier treatment versus nephrectomy reemerged as a source of controversy.

Although nephrectomy alone clearly offered no curative benefit in the setting of metastatic disease (11), cytoreductive surgery was proposed to have a role when done in conjunction with cytokine therapy. More than a decade was required to resolve this question for most investigators. A number of early studies on prognostic factors in RCC suggested that undergoing nephrectomy was associated with improved survival (15, 16). Potential disadvantages included perioperative morbidity and mortality, as well as delay in starting systemic therapy. Consistent with these concerns, other early studies suggested that a significant percentage of patients were noted to have disease progression that prevented them from receiving immunotherapy after undergoing surgery. For example, Bennett et al. (17) reported on a series of 30 patients with metastatic RCC who underwent nephrectomy in preparation for systemic therapy. Of these patients, 77% had disease progression or surgery-related morbidity or mortality that prevented the subsequent administration of interleukin-2 (IL-2) after nephrectomy. These studies led to a reevaluation of eligibility criteria and stricter criteria for determining whether cytoreductive nephrectomy was appropriate for a given patient (18).

Overall, these retrospective single-institution studies showed favorable response rates of 18% to 39%, with a median overall survival of 12 to 20.5 months (19–22). One such study from University of California at Los Angeles of 203 metastatic RCC patients treated with various combinations of IL-2 immunotherapy regimens with and without adjunctive nephrectomy attempted to delineate the specific benefit that adjunctive nephrectomy can provide and to determine the factors that maximize the effects of immunotherapy (23). The study reported an overall 3-year survival rate of 31%, with the highest survival rates in patients treated by cytoreductive nephrectomy followed by immunotherapy, and found that the worst outcomes were achieved in those patients undergoing immunotherapy with their primary tumor in place (3-year survival rate, 4%). These results were later expanded to an evaluation of 335 patients, which showed 1- and 2-year survival rates of 29% and 4% for patients treated with IL-2 and their primary tumor in place and 67% and 44% for patients receiving any kind of immunotherapy after adjunctive nephrectomy (24).

The best evidence for performing cytoreductive nephrectomy before cytokine therapy came from two prospective randomized clinical trials, Southwest Oncology Group (SWOG) 8949 and European Organization for Research and Treatment of Cancer (EORTC) 30947 (9, 10), which revealed a survival benefit for nephrectomy followed by IFN-α compared with IFN-α alone (median survival of 11.1 and 8.1 months, respectively, in the SWOG trial and 17 and 7 months, respectively, in the EORTC trial). Flanigan et al. (8) did a combined analysis of these two trials, which yielded a median survival of 13.6 months for nephrectomy plus IFN-α versus 7.8 months for IFN-α alone. Cytoreductive nephrectomy seemed to improve overall survival in patients with metastatic RCC treated with IFN-α independent of patient performance status, site of metastases, and presence of measurable disease. A retrospective study recently reported by Han et al. (25) showed that patients with more than one metastatic site had a lower response rate to adjuvant immunotherapy after nephrectomy of the primary tumor and a significantly shorter survival than patients with a single metastatic site. Although the observed survival benefit in the SWOG and EORTC Genitourinary Group studies was independent of the location of metastatic sites, neither trial stratified the number of metastatic sites or overall tumor burden, and therefore this question remains unresolved.

Investigators at University of California at Los Angeles supplemented the SWOG findings with retrospective data to address the relative efficacy of IFN-α versus IL-2 after cytoreductive nephrectomy using a comparable population treated with IL-2 from the University of California at Los Angeles Kidney Cancer Database, which conatins the records of more than 450 metastatic RCC patients treated with immunotherapy (26). Using the eligibility criteria for the SWOG 8949 study, 89 patients treated with IL-2-based regimens after nephrectomy were identified. Survival of these patients was analyzed and compared with the survival of 120 patients in the SWOG surgery arm. Median survival of the patients treated with nephrectomy plus IL-2 was 16.7 months, which was twice that of the IFN-α only SWOG arm, and 4 months (30%) greater than the nephrectomy plus IFN-α SWOG arm. At 5 years, the survival rate was 19.6% for patients who received IL-2 compared with 10% for those who received IFN-α.

The mechanisms involved that underlie the survival benefit of cytoreductive nephrectomy are still not clearly understood. A number of hypotheses are generally offered, ranging from the simplistic notion that removal of a symptomatic local tumor may improve performance status and therefore improve prognosis, that reduction in tumor burden itself may enhance the potential of an immune-mediated response to systemic treatment, that removal of the tumor actually benefits the patient as a surrogate for removal of a source of growth factors, immunosuppressant cytokines, and other molecules that underlie paraneoplastic symptoms such as cachexia, and that nephrectomy removes a source of future additional metastases (10, 27).

None of these explanations has been satisfactorily examined. A provocative study arose from SWOG 8949 that examined the role of postoperative azotemia resulting from cytoreductive nephrectomy in enhancing survival, with the interesting hypothesis that it is the removal of the kidney and not the removal of the tumor that should be credited (28). It has been

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long known that many tumors acidify their peritumoral microenvironment as a means of overcoming the negative effects of the intracellular acidosis that results from tumor cell hypoxia and increased glycolytic metabolism. Mathematical models based on graded systemic metabolic acidosis associated with mild renal failure (there was a 20% increase in blood urea nitrogen and creatinine in the SWOG patients) suggest that unilateral nephrectomy may alter the dynamics of the tumor-host interface and further acidify the tumor pH sufficiently to exceed the tolerance of tumor cells, slowing or reversing tumor growth and invasion. In this interesting report, which looked at the surgical arm of the SWOG study, patients experiencing postoperative increase in blood urea nitrogen and creatinine had a significantly improved survival (17 versus 4 months) compared with those who did not ($P = 0.0007$).

The Era of Targeted Therapy

The approval of two new targeted agents for metastatic RCC by the U.S. Food and Drug Administration (FDA) in 2005-2006 marks the beginning of a new era in the management of RCC. Sorafenib (BAY 439006) is orally bioavailable and was developed initially for its inhibitory effects on Raf-1, but further activity was shown against additional receptor tyrosine kinases in both the tumor cell and tumor vasculature, including vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor, FLT-3, and c-KIT. With its approval on December 20, 2005 by the Food and Drug Administration, sorafenib became the first Food and Drug Administration–approved treatment for advanced RCC in more than a decade. This approval was based on the demonstration of improved progression-free survival in a large, multinational, randomized, double-blind, placebo-controlled phase 3 study and a supportive phase 2 study. The median progression-free survival was 167 days in the sorafenib group versus 84 days in the placebo control group (hazard ratio, 0.44; 95% confidence interval, 0.35-0.55; log-rank $P < 0.000001$; ref. 29). Sunitinib malate is another oral multikinase inhibitor that targets the phosphorylase activity of several receptor tyrosine kinases, including the vascular endothelial growth factor receptor, platelet-derived growth factor receptor, KIT, and FLT-3 tyrosine kinases. Approval of sunitinib for the treatment of advanced RCC was based on the results of a pair of single-arm, multicenter studies. The first study enrolled 106 patients in whom prior cytokine therapy had failed. The trial was designed to investigate the objective response rate of sunitinib therapy. The second study used a similar design to trial 1, treating 63 RCC patients in whom cytokine therapy failed. Data indicate that sunitinib induces a partial response, stable disease, and progressive disease in 15 (24%), 29 (46%), and 19 (30%) patients, respectively (30). In January 2006, the Food and Drug Administration granted accelerated approval for sunitinib in the treatment of patients with advanced RCC. In contrast to its approval for gastrointestinal stromal tumors, which was based on the ability of sunitinib to delay the growth of tumors, this approval was based on the partial response rate of sunitinib and its duration of response.

With these dramatic advances in the treatment of advanced RCC, the questions surrounding the necessity and benefit of nephrectomy before targeted therapies have reemerged as clinically relevant controversies. These questions are legitimate. Two main camps are forming: evidence-based literalists who see the proven benefits of these agents to be shown only in the setting of postnephrectomy patients and medical nephrectomists who believe that the new agents obviate the need for nephrectomy. The former point to the sunitinib phase 2 studies, in which 100% of patients were treated after progression with cytokine therapy and 97% of patients' previous treatment included cytoreductive nephrectomy (100% of patients treated in the larger of the two phase 2 studies). Similarly, in the sorafenib phase 3 study, 82% of patients were treated after progression with cytokine therapy, including IL-2 (44%) and an IFN (68%), and 94% of patients' previous treatment included cytoreductive nephrectomy. The latter point to radiographs from the sorafenib and sunitinib studies, which show notable reductions in the size of metastatic and primary lesions (in select cases). Unfortunately, at present, there is no valid basis on which one can deduce the relative contribution cytoreductive nephrectomy makes to the benefits shown for these new targeted agents.

Conclusions

Before the availability of effective systemic treatment for advanced RCC, nephrectomy did not contribute to patient survival, and surgery was confined to the realm of palliative therapy. With the introduction of immune-based agents, nephrectomy was shown to improve survival when done before cytokine therapy in wisely selected patients. The era of molecularly targeted therapy has just begun and will continue to play an important role in the management of advanced RCC for the foreseeable future. The valid clinical question of whether to remove the primary tumor before targeted therapy is one that, at present, has no answer and will become increasingly common, affecting thousands of patients. The initiation of a phase 3 study to compare the survival of patients treated by nephrectomy plus targeted therapy with the survival of patients treated by targeted therapy alone, with nephrectomy reserved for clinical indications, should be considered to answer these questions. Until evidence from such a study becomes available to guide physicians, and without evidence to the contrary, cytoreductive nephrectomy should be considered to have shown a survival benefit and should be used in appropriately selected patients with metastatic RCC receiving postsurgical systemic therapies.

Open Discussion

Dr. Atkins: Could removing the primary kidney tumor affect the efficacy of antiangiogenic therapy?

Dr. Pantuck: The primary may be making angiogenic factors, but just as easily the primary tumor often makes antiangiogenic factors that can inhibit metastases.

Dr. Rini: In terms of a randomized trial, we have a therapy, debulking nephrectomy, which, in two prospective randomized trials in a combined analysis, has a 5-month survival advantage. I would have a hard time randomizing patients to an arm that does not include that therapy.

Dr. Figlin: I am puzzled why the targeted therapy-only arm in the absence of nephrectomy would be ethically unacceptable. If these agents are working systemically, and you have removed from that patient population people who require a

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nephrectomy for palliative purposes, why do the prior trials dictate the need for surgery in the new era of targeted agents?

Dr. Sosman: If we had endless numbers of patients, it would be a good experiment to examine the role of nephrectomy. However, we have limited patients, plus I do not think a phase 3 study is reasonable. A phase 2 study would be preferable.

Dr. Pantuck: There is no question that some patients will do better in terms of performance status and quality of life when they have large tumors that are symptomatic and causing problems. I am not arguing that nephrectomy in that setting does not provide a benefit.

Dr. Rini: In somebody with a small primary, we could make the argument that debulking nephrectomy may not be beneficial. Appropriately selected patients is key.

Dr. Pantuck: A phase 2 study is obviously easier to do than a phase 3 study because it is one arm and requires fewer patients. My hesitation is that nobody will believe it because it is not randomized and controlled.

Dr. Flaherty: Some of the patients I have treated with sorafenib the longest have not had a prior nephrectomy, because their primary tumors constitute about 80% of their target lesion volume. For these patients to achieve a response or progress by Response Evaluation Criteria in Solid Tumors criteria is hard. They do not change as much in terms of their target tumor volume compared with patients who just have lung nodules. The best way to wreck a response rate or to artificially prolong progression-free survival is to include patients who have not had prior nephrectomy because those patients had a big target lesion that contributes to 80% of their measurement.

Dr. Rini: You would have to look at the measurements both with and without the primary.

Dr. Flaherty: That would be more meaningful.

Dr. Atkins: The argument in immunotherapy was always that the primary tumor somehow influenced the response of the metastatic disease to immunotherapy, not that it influenced the measurements. We are unsure whether that paradigm applies to targeted therapy. I think a phase 2 study in selected patients with relatively small tumor burden in primary tumor compared with metastatic disease burden who are not being considered as candidates for immunotherapy should be performed. We could ascertain the effect of therapy on the metastases and the primary tumor and see whether they are similar.

Dr. Kaelin: I think it would be a complete waste of time and money to do a one-arm phase 2 study. What are you looking for? I know it is feasible to treat the patients without doing the nephrectomy. Also, there is no biologically compelling reason that the response rate will be different between the primary site and metastases.

Dr. Atkins: The question is not "Does this prolong survival?" but "Does the primary tumor respond and does it respond in the same way as the metastatic lesions?"

Dr. Wood: But it's not just a question of shrinking the tumor; it's a question of the biology of the tumor.

Dr. Pantuck: I'm also not concerned about shrinking the primary tumor. The question is can you match the efficacy in terms of disease-free progression.

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