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Integration of Surgery and Systemic Targeted Therapy in the Management of Patients with Metastatic Renal Cell Carcinoma

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Surgery has always played a major role in the treatment of renal cell carcinoma. It is often curative in the setting of localized and locally advanced disease, and served as an adjunctive treatment in the management of patients with metastatic renal cell carcinoma. Based largely on the observation that the primary tumor rarely responded to systemic therapy, cytoreductive surgery became part of the multidisciplinary approach to the treatment of patients with metastatic renal cell carcinoma, in concert with planned immunotherapy with interleukin 2 or interferon. The survival benefit to patients with this approach was validated in two phase III randomized clinical trials. But now, the treatment landscape has changed dramatically, with the introduction of targeted agents, and some have questioned whether or not cytoreductive surgery still remains an important part of patient management. In fact, the Carmena Trial, ongoing in France, is designed to ask whether sunitinib alone is not inferior to cytoreductive nephrectomy followed by sunitinib. While we await the results of this trial, we are still left with the difficult task of managing patients with metastatic renal cell carcinoma in the era of targeted therapy and must let available evidence guide a rational approach to treatment.

The available evidence would suggest that cytoreductive surgery, and metastasectomy for that matter, should remain as important part of the management of patients with metastatic disease. Treatment with targeted therapy results in few, if any, complete responses, and the primary tumor does not reliably respond to therapy. Resistance to targeted therapy is an inevitability such that surgical resection remains the only mechanism for substantial tumor reduction in properly selected patients. The vast majority of patients enrolled in the clinical trials to test the efficacy of targeted therapy had a previous nephrectomy, so one could argue that their efficacy is in the context of prior nephrectomy. Further, retrospective analysis of expanded access programs suggest that patients with prior nephrectomy demonstrate a better progression free and overall survival when compared to patients treated with their primary tumor in situ. All of these data points argue for the role of cytoreductive surgery in the management of properly selected patients with metastatic disease.

A novel treatment paradigm that is being tested at the University of Texas M. D. Anderson Cancer Center, as well as other centers, is the concept of presurgical therapy. In this treatment paradigm, patients that are upfront surgical candidates are given limited courses of systemic targeted therapy, prior to surgery. The premise of this approach is that it will allow us to better select patients responding to targeted therapy for cytoreduction, and may also provide the benefit of reducing surgical morbidity through primary tumor downstaging. In addition, and perhaps most importantly, it serves as a litmus test, or selection process, to avoid what can be highly morbid surgery in patients not destined to respond to systemic therapy. While this approach has shown some initial promise, further study through clinical trials is warranted to validate its efficacy. Till that time, upfront cytoreductive surgery in properly selected patients with metastatic renal cell carcinoma should remain the standard of care.