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Systemic therapy following metastasectomy for renal cell carcinoma: Using insights from other clinical settings to address unanswered questions

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Abstract

Surgical resection for metastatic renal cell carcinoma (RCC) was first described several decades ago, but the appropriate role for surgery in coordinated multidisciplinary care has not been well-defined. The explosive development of new therapies for advanced RCC over the past 10 years has improved the outlook for patients, and there is now renewed interest in surgical metastasectomy for selected patients with metastatic RCC, moving away from the conventional dichotomy between surgery for local disease and systemic therapy for metastatic disease. Patients rendered disease-free after metastasectomy are at high risk of recurrence, but to date no postoperative medical treatment has been shown to be beneficial. Ongoing studies and relevant data will be reviewed to frame the multidisciplinary approach to patients with oligometastatic RCC and to outline future challenges and opportunities for advancing their care. © 2017 Published by Elsevier Inc.

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Introduction

The last 2 decades have witnessed an explosive development of new therapies for advanced cancer, including entirely new classes of agents beyond traditional cytotoxic chemotherapeutics. Monoclonal antibodies, small molecule kinase inhibitors, immune checkpoint inhibitors, and cancer vaccines have all shown benefit across a range of human malignancies. Specifically, for metastatic renal cell carcinoma (mRCC), an unprecedented 10 new agents were approved for advanced disease in the last decade alone. An exciting challenge facing the field today is the integration of these novel treatments into established therapeutic regimens. In particular, the ability to integrate emerging systemic agents with surgical resection offers the greatest potential for optimal outcomes. This has renewed interest in a role for surgery in management of selected patients with mRCC, moving away from the conventional dichotomy between surgery for local disease and systemic therapy for metastatic disease. With aggressive surgical resection, it is not uncommon to remove all radiographically evident disease. However, these patients remain at high risk (HD) of recurrence, and there is a compelling unmet need for strategies to mitigate this risk. The selection of appropriate patients for metastasectomy and optimal sequencing and timing surgery and medical treatment is not yet known. These questions are the focus of ongoing research efforts and of this review.

RCC: Background and perspective

Approximately, 70% of patients with RCC are diagnosed with early stage, localized disease, and can be treated with definitive surgical resection. Long-term freedom from disease is achieved in 70%, depending on pathological stage. Unfortunately, approximately one-third present with metastatic disease at the time of diagnosis. Patients with advanced or recurrent RCC rarely achieve long-term disease control and are generally managed with systemic therapy.

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Median survival in modern series is approximately 2 years with wide variance: some patients living less than 6 months and others more than 5 years [1]. Prognostic models based on clinical and laboratory studies are helpful in predicting overall survival in these patients [1,2]. Rare spontaneous tumor regression and late recurrences suggest a role for antitumor immunity in the natural history of the disease.

Surgery for mRCC

Whereas resection of localized cancer is often curative across a spectrum of solid tumors, surgery for metastatic disease has historically been considered to be of limited benefit beyond palliation. Recent observations have renewed interest in the role of cytoreductive removal of the primary tumor and metastasectomy for these patients. A role for metastasectomy has been demonstrated for multiple advanced solid tumors, including breast [3], colorectal [4], urothelial [5], and other cancers. Surgical resection of mRCC was first reported in the medical literature in 1939 [6], and many case series of patients treated with metastasectomy have been published through the years with 5-year survival ranging from 16%–88% [7–15]. Sites of metastasis reported include lung, liver, adrenal, pancreas, bone, brain, and thyroid. However, no randomized study has examined the benefit of metastasectomy. A disease-free interval greater than 1 year from prior nephrectomy and solitary site of metastasis were shown on multivariate analysis to be strongly predictive for survival following metastasectomy [7].

Systemic therapy for mRCC

Systemic therapy is the mainstay of treatment for mRCC. Cytotoxic chemotherapy has limited activity in this disease. Immunotherapy has been investigated for mRCC for many decades, and high-dose (HD) interleukin-2 (IL-2) therapy was approved for advanced RCC by the US FDA in 1992, based on durable complete remissions in 5%–10% of patients [16]. However, the toxicity of this inpatient regimen has limited its use to the fittest patients and to experienced centers.

In the last decade, a series of agents targeting the vascular endothelial growth factor (VEGF), and the mammalian target of rapamycin (mTOR) molecular signaling pathways were developed based upon the importance of these pathways in RCC molecular pathogenesis. The VEGF receptor tyrosine kinase inhibitors (TKI) sorafenib (2006) [17] and sunitinib (2007) [18] were approved after demonstrating objective clinical responses and delayed disease progression. Two small molecule inhibitors of the mTOR kinase, temsirolimus and everolimus, were subsequently approved [19,20] in the first-line, poor-risk, and the second-line setting, respectively. The anti-vascular endothelial growth factor receptor (VEGFR) monoclonal antibody, bevacizumab, was approved for mRCC in combination with subcutaneous IFN-α [21,22]. Four additional TKI targeting VEGFR and other receptors, pazopanib [23], axitinib [24], cabozantinib [25], and lenvatinib (in combination with Everolimus) [24], are also approved for mRCC.

Most recently, immune checkpoint inhibitors have shown clinical activity in mRCC. The anti-programmed cell death protein-1 antibody, nivolumab, was approved for second-line use based upon superior overall survival compared with everolimus [26]. A large phase 3 study is currently underway to test the combination of nivolumab plus the anti-CTLA4 antibody, ipilimumab vs. sunitinib in untreated mRCC (NCT02231749). Additional combination studies including immune checkpoint inhibitors are underway.

Cytoreductive nephrectomy in mRCC

Cytoreductive nephrectomy (removal of the primary tumor in patients with inoperable mRCC) followed by systemic therapy has been more extensively studied than metastasectomy for mRCC, and will be discussed here as a paradigm for multidisciplinary treatment. For most solid tumors, surgical resection of the primary tumor is not a standard oncologic practice for patients presenting with synchronous metastatic disease [27]. Recent studies, however, have reexamined the role of cytoreductive surgery for advanced solid tumors. Although the benefit of cytoreductive surgery is debatable for other solid organ tumors, cytoreductive nephrectomy for RCC has been performed for many decades, and has been associated with spontaneous regression of metastatic disease in individual cases [28,29]. Two randomized trials showed an overall survival benefit to cytoreductive surgery followed by IFN-α compared with IFN-α alone [30–32]. Although the mechanism by which cytoreductive nephrectomy exerts its survival benefit is unknown, it has been hypothesized that the benefit of surgery may be explained by decreased tumor-related immunosuppression facilitating the activity of IFN-α. Although this hypothesis might explain the advantage of cytoreductive nephrectomy for patients treated with immunotherapy, it is less clear that a similar benefit would be achieved before the targeted therapies used today. To address this question, retrospective analyses have shown a clinical benefit to cytoreductive nephrectomy before targeted therapy [1]. A randomized study to address the role of cytoreductive nephrectomy before sunitinib is currently enrolling subjects (NCT00930033). Another contemporary randomized study evaluated the effect of a tumor-derived vaccine in combination with sunitinib vs. sunitinib alone following cytoreductive nephrectomy. Although the full results have not been published, a press release indicated that the data safety monitoring committee recommended halting the trial since it was unlikely that an overall survival benefit to the vaccine would be seen [33]. This study, however, provides proof of principle that surgery and immunotherapy can be successfully coordinated in a multicenter clinical trial.