The Evolving Role of Cytoreductive Surgery for Metastatic Renal Cell Carcinoma

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In this issue of ONCOLOGY, Chaudhary and Hull succinctly summarize historical trends and current thinking regarding the role of cytoreductive nephrectomy in patients with metastatic kidney cancer. Before the era of immunotherapy, there was little evidence that the natural history of metastatic renal cell carcinoma was improved by cytoreductive nephrectomy.[1] Patients with metastatic cancer generally die from complications related to their sites of tumor spread and not from the primary tumor; thus, on face value, it seems illogical to surgically remove the primary tumor in these patients. Nevertheless, despite its apparent failure to improve survival, nephrectomy has always had an unchallenged role in symptom palliation and was often recommended for patients with bleeding, pain, or hypercalcemia to improve their quality of life. With the emergence of modern immunotherapy, the role of nephrectomy and the relative efficacy of initial cytokine treatment vs nephrectomy has reemerged as a source of controversy. The question surrounding the sequence of treatment involved the surgical recovery time and whether this time allowed for progression of disease by hindering the timely delivery of systemic therapy. As summarized by Chaudhary and Hull, several large series of metastatic patients have indicated that nephrectomy has a positive impact on survival.

Survival Data

Retrospective data from the University of California, Los Angeles (UCLA) demonstrated 1- and 2-year survival rates of 29% and 4% among patients treated with interleukin-2 (IL-2, Proleukin), with their primary tumor in place. These survival rates were significantly lower than the 1-year (67%) and 2-year (44%) survival rates of patients who received immunotherapy following cytoreductive nephrectomy.[2] However, the best evidence supporting the use of cytoreductive nephrectomy comes from two prospective, randomized, phase III trials—one American and one European.[3,4] Both trials showed that median survival improved significantly in the surgical arm, with increases ranging from 4 to 10 months.

Prognosis and Performance Status

Although randomized, controlled trials remain the surest foundation for evidence-based medical practice and clinical decision-making, several caveats concerning performance status should be considered before we unequivocally recommend nephrectomy for every patient with metastatic kidney cancer. First, despite randomization, the Southwest Oncology Group (SWOG) study assigned more patients with a performance status of 0 to the nephrectomy arm. Performance status is a crucial prognostic factor for patients with metastatic renal cell carcinoma,[5] and in the SWOG study, survival differed to a greater degree between patients with a performance status of 0 (15 months) and those with a performance status of 1 (6 months) than between the two treatment arms. However, the survival benefit associated with nephrectomy remained when patients were substratified according to performance status, thus reaffirming that the study’s conclusion was genuine and not simply a consequence of faulty randomization. Second, because these studies involved only patients with good performance status who were treated by experienced surgeons and oncolohistory gists, the applicability of these results to the general population with metastatic renal cell carcinoma raises concerns. There is no easy substitute for clinical judgment, and no basis for recommending nephrectomy to patients with a lower performance status who are less likely to tolerate surgery and remain well enough to ever receive systemic treatment.

Beneficial Mechanisms

The mechanisms that underlie the survival benefit of cytoreductive nephrectomy are not clearly...
understood. Several hypotheses are generally offered including (1) that removal of a symptomatic local tumor may improve performance status and therefore improve prognosis, (2) that a reduction in tumor burden itself may enhance the potential of an immunemediated response to systemic treatment, (3) 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 (4) that nephrectomy removes a source of future additional metastases. However, none of these explanations has been satisfactorily examined. Recently, a provocative study examined the role of azotemia in enhancing survival following cytoreductive nephrectomy, with the interesting hypothesis that removal of the kidney, and not removal of the tumor, should be credited.[6] It has long been 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 (SWOG patients showed a 20% increase in blood urea nitrogen [BUN] and creatinine) 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. This, in effect, slows or reverses tumor growth and invasion. In this interesting report, patients in the surgical arm of the SWOG study who experienced a postoperative increase in BUN and creatinine had a significantly improved survival compared to those who did not (17 vs 4 months, \( P = .0007 \)).

**Carbonic Anhydrase IX**

These authors, however, did not consider the possible role of carbonic anhydrase IX in this process. Carbonic anhydrase IX is a transmembrane enzyme that is capable of catalyzing the reversible hydration of CO\(_2\) to form HCO\(_3^-\) and H\(^+\),[7,8] and thus, is thought to play a key role in the regulation of intra- and extracellular pH. It has been proposed that carbonic anhydrase IX allows tumors to adapt to an acidic and hypoxic environment, thereby promoting further proliferation and metastasis of cancer cells. The expression of carbonic anhydrase IX is directly linked to kidney cancer through its relationship to loss of von Hippel-Lindau gene function. This, in turn, causes stabilization of the hypoxia-inducible factor-1-alpha, the products of which are critical components of tumor angiogenesis (eg, vascular endothelial growth factor), glucose transport (eg, glut 1, glut 3), glycolysis (eg, 6-phosphofructose 2-kinase), pH control (eg, the carbonic anhydrase family), and apoptotic (eg, bid, bax, and bad) pathways.[9] Immunohistochemical studies of malignant and benign renal tissues revealed that carbonic anhydrase IX-the only well-described tumorassociated antigen for the disease- is highly expressed in renal cell carcinoma, suggesting that it is one of the most significant molecular markers described in kidney cancer to date. Moreover, the enzyme may be useful as both a diagnostic biomarker and target of therapy. At UCLA, immunohistochemical analysis using a carbonic anhydrase IX monoclonal antibody was performed on tissue microarrays from patients who were treated with nephrectomy for clear cell carcinoma of the kidney.[10] Carbonic anhydrase IX staining was present in 94% of clear cell renal adenocarcinomas, and its level of expression was correlated with response to treatment, clinical factors, pathologic features, and survival. Low-level carbonic anhydrase IX staining was an independent poor prognostic factor for survival among patients with metastatic renal cell carcinoma, and marker measurements could be used to significantly stratify patients with metastatic disease when analyzed by T stage, Fuhrman grade, nodal involvement, and performance status.

**Conclusions**

Chaudhary and Hull aptly summarize the current data leading to the conclusion that for appropriately selected patients with metastatic kidney cancer and good performance status, cytoreductive nephrectomy should be offered as part of multimodality treatment including adjuvant systemic immunotherapy. The mechanisms for improved survival are currently not well understood, but may be related to fundamental molecular issues relating to the genetics of renal cell carcinoma.

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**References:**


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