The Evolving Role of Cytoreductive Surgery for Metastatic Renal Cell Carcinoma

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Metastatic renal cell carcinoma is a devastating disease associated with poor survival. Immunotherapy is the mainstay of treatment, but response rates are low. The role of cytoreductive surgery in the presence of metastatic disease is evolving. From both retrospective and recently published randomized clinical trials, it is now apparent that among patients with metastatic renal cell carcinoma and good performance status, cytoreductive surgery followed by immunotherapy improves survival. However, this approach is likely to be detrimental in patients with poor performance status. Clinical trials of novel agents remain a priority in this disease.
Source:

It is estimated that more than 31,000 cases of renal cell carcinoma will be diagnosed in the United States in 2003, and that about 19,000 deaths will result from this disease.[1] Approximately 30% to 40% of patients present with metastatic disease, and an additional 30% to 40% who present with localized or locally advanced disease subsequently develop metastases.[2] About 30% of patients have detectable metastasis at the time of initial presentation and may have symptoms referrable to local involvement. Despite extensive research, systemic therapy for metastatic renal cell carcinoma has produced discouraging results. The disease is chemoresistant, and no agent consistently achieves a response in more than 10% of patients.[3] Prognosis remains guarded, with median survival ranging from 6 to 12 months in patients with metastatic disease. ***Immunologic Therapy***
Immunologic therapy has assumed a predominant role in the treatment of advanced renal cell cancer. Several observations concerning its natural history suggest that modulation of the immune system may be an important component in controlling the disease. These include late relapses after nephrectomy, rare spontaneous regression, T-cell-mediated immune responses, response to biologic agents, and prolonged stabilization of metastatic disease without treatment. Immunotherapy with the cytokines interleukin or interferon produces responses in about 10% to 20% of patients. Small numbers of patients achieve complete or partial responses, but most do not respond, and few survive long term.[4] **Interleukin-2**
The predominant interleukin used in patients with metastatic renal cell carcinoma is interleukin-2 (IL-2, Proleukin), which enhances the proliferation and function of T lymphocytes.High-dose bolus IL-2 at doses ranging from 600,000 IU/kg to 720,000 IU/kg has achieved objective responses in 37 (15%) of 255 patients with 17 (7%) complete responses and 20 (8%) partial responses. Long-term follow-up demonstrates that 10% of all treated patients remain alive and free of disease, and nearly half of responding patients remain in clinical remission.[5] Based on the curative potential of these responses, the US Food and Drug Administration approved IL-2 for the treatment of metastatic renal cell carcinoma. High-dose bolus IL-2 may lead to vascular leak syndrome, hypotension, pulmonary edema, and a variety of infectious complications. Moreover, initial trials reported a 2% to 4% mortality rate. In recent reports, mortality rates have decreased considerably, although the expense of the intensive care unit, need for trained medical staff, and the nature of the toxicities have led investigators to look for simpler outpatient regimens. **Interferon-alpha**
Interferon-alpha, another cytokine, is also used widely in patients with renal cell carcinoma. It demonstrates potent immunomodulatory, antiproliferative, and antiviral properties. Interferon modulates host immune responses by activating mononuclear cells, inducing expression of major histocompatibility complex antigens, and enhancing cytototoxic lymphocyte activity.
Interferon-alpha can also produce tumor regression in about 12% to 15% of patients with metastatic renal cell carcinoma. Complete responses occur in 2% to 5% of patients and are generally seen in those with pulmonary metastases.[6] ***Radical Nephrectomy in Metastatic Disease*** **Palliative Nephrectomy**
Fortunately, it is unusual for patients with metastatic renal cell carcinoma to present with severe symptoms from their primary tumor. However, flank/abdominal pain, gastrointestinal symptoms, intractable gross hematuria, and paraneoplastic syndromes do occur and warrant therapy. Palliative nephrectomy may provide benefits and resolve any paraneoplastic syndromes, but the median

survival of patients who undergo palliative nephrectomy only ranges from 4 to 12 months, if not followed by biologic response modifiers.[7] **Radical Nephrectomy and Metastectomy**
Patients presenting initially with surgically resectable metastatic disease should be considered for simultaneous resection of the primary tumor and the metastases. Several studies have reported long-term survival with this approach, and indeed, survival appears to be superior with complete excision of metastatic lesions, as compared with cytoreductive surgery followed by immunotherapy alone (without excision of metastatic lesions).[8,9] The ideal candidates for these resections are patients with pulmonary metastases. Recently, Piltz et al reported the longterm follow-up of patients after pulmonary resection of renal metastases. Survival at 3, 5, and 10 years was 54%, 40%, and 33%, respectively.[10] The Mayo Clinic group reported on a series of 41 patients, 88% of whom underwent complete excision of all metastatic disease and the primary tumor; 64% of these patients had a single metastatic lesion. The 5-year survival rate was reported to be 31%.[11] Data from two modern series addressing resection of hepatic metastases from colorectal cancer have shown that the procedure is safe and provides 3-year survival rates of approximately 33% to 46%.[12,13] Unfortunately, no large anecdotal series on hepatic resections of renal metastases exist, but based on a review of the available anecdotal literature, these resections appear to be safe and justified.[14] Prospective randomized data are still not available. In regard to surgical excision of metastatic lesions to the adrenal gland, again, the only available data are anecdotal. There appears to be a dichotomy regarding the survival benefit associated with excision of these metastases. Adrenal metastases occur only in approximately 3% of patients in large series.[15] Several authors have questioned whether complete excision improves the prognosis of these patients.[15,16] However, if we adhere to the principles of cytoreductive surgery, every attempt should be made to remove all gross disease at the time of excision of the primary tumor. In the case of metachronous metastases to the contralateral adrenal gland, adrenalectomy appears to provide some long-term survival benefit.[17] In conclusion, anecdotal evidence supports the use of radical nephrectomy in combination with resection of metastasis in patients with metastatic renal cell carcinoma. The patients who seem to benefit most are those with solitary pulmonary metastases. ***Cytoreductive Surgery*** In the 1970s, several large series of patients underwent radical nephrectomy in the face of metastatic disease with the hope of inducing a spontaneous regression. Unfortunately, the rates of spontaneous regression were less than 1%, and survival benefits did not outweigh the increased morbidity and mortality associated with primary nephrectomy.[18,19] The authors concluded that debulking nephrectomy was not justified. With the advent and efficacy of biologic response modifiers, we have seen renewed interest in cytoreductive surgery for patients with metastatic renal cell carcinoma. The timing of cytoreductive surgery-either before or after immunotherapy-has generated controversy in the past. However, with data from retrospective studies and recently from randomized trials, it has become apparent that cytoreductive surgery followed by immunotherapy is beneficial in selected groups of patients with good performance status.[8,9,20] **Disadvantages of Cytoreductive Surgery Followed by Immunotherapy**
Cytoreductive surgery followed by immunotherapy has two theoretical disadvantages. First, metastatic disease could grow during convalescence from surgery. However, in the most recent cytoreductive series, the time between surgery and the initiation of systemic therapy was decreased to 2 to 6 weeks. Given this short period between therapies, it would seem unnecessary to delay cytoreductive surgery until after immunotherapy. Second, it was debated in the past that the morbidity and/or mortality of the surgery may preclude treatment in a significant percentage of patients. However, in two recent series, the operative mortality rate was only 1%, and the majority of patients

Table 1

Randomized Trials of Cytoreductive Surgery Followed by Interferon Alfa-2b vs Interferon Alfa-2b Alone

EORTC 30947 (85 patients)	Operative Mortality	Complete Response + Partial Response	Time to Disease Progression	Median Survival
Cytoreductive surgery plus interferon alfa-2b (42 patients)	0%	8/42 (19%)	5 mo	17 mo
Interferon alfa-2b (43 patients)		5/43 (12%) *P* = .38	3 mo Hazard ratio = 0.60 (95 % CI = 0.36–0.97)	7 mo Hazard ratio = 0.54 (95% CI = 0.31–0.94)
SWOG 9498 (241 patients)				
Cytoreductive surgery plus interferon alfa-2b (120 patients)	< 1%	3/92 (3.3%)	Not reported	11.1 mo
Interferon alfa-2b (121 patients)		3/83 (3.6%)	Not reported	8.1 mo *P* = .05

CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; SWOG = Southwest Oncology Group.

were able to receive systemic therapy.[8,9,20] In the Southwest Oncology Group (SWOG) 8949 trial, 98% of patients who underwent nephrectomy received immunotherapy. Therefore, the theoretical disadvantages of cytoreductive surgery prior to the initiation of systemic therapy do not seem to justify delaying the surgery. However, patients in these series were selected for good performance status. Further justification for cytoreductive surgery prior to systemic therapy is based on the low response rate of the primary renal tumor to immunotherapy.[21] **Advantages of Cytoreductive Surgery Followed by Immunotherapy**

There can be several potential advantages to performing cytoreductive surgery prior to the initiation of immunotherapy. Renal cell carcinomas produce large amounts of both proinflammatory and T-cell-inhibitory cytokines that could potentially influence the immune response of the host, especially tumor-specific cytotoxic T cells.[22] Animal studies have established that adoptive immunotherapy is most beneficial with decreased tumor burden.[23] In addition, immunoreactive cells can be obtained for research purposes and may prevent further seeding of metastases. Clinically, cytoreductive surgery may prevent complications during systemic treatment, prevent local symptoms of pain and bleeding with an improvement in performance status, and lead to better tolerance and higher response rates to immunotherapy. **Retrospective Studies**

Cytoreductive surgery followed by immunotherapy has been well documented in several retrospective studies.[20,24-27] In the largest published report from the National Cancer Institute, 195 patients underwent cytoreductive surgery before high-dose IL-2 therapy over an 11-year period. The primary site and adjacent locoregional metastatic disease were resected, with a perioperative mortality rate of only 1%. After surgery, 62% of patients (121 of 195) were eligible to receive high-dose bolus IL-2; 55% (107 of 195) were eligible for immune- based therapy, and 22.6% (44 of 195) developed disease progression in the 8-week recovery period. Objective responses were reported in 19 (18%) of 107 patients, with 4 complete and 15 partial responses.[20] Spontaneous regression of pulmonary metastasis occurred in four patients (2%) after cytoreductive surgery. In another study, investigators from the University of California, Los Angeles (UCLA) reported on 63 newly diagnosed patients with metastatic renal cell carcinoma who successfully underwent radical nephrectomy followed by consideration for adoptive immunotherapy with IL-2, interferon- alpha, and tumor-infiltrating lymphocytes. No cases of postoperative mortality were reported. A total of 56 patients (88%) were able to receive immunotherapy. Among these patients, the response rate was 33.9%, and the 2-year survival rate was 43%.[24] In a retrospective investigation by Naitoh[25] in 31 patients with metastatic renal cell carcinoma and extensive disease involving the inferior vena cava, 80% were able to complete a full course of surgery and immunotherapy. In 90% of patients, the tumor thrombus extended below the diaphragm, and 23% had isolated pulmonary metastases. Although no postoperative deaths occurred, three patients died within 1 month after cytoreductive surgery. Overall, the actuarial 5-year survival for this poorrisk subgroup was 17%. Patients with isolated pulmonary metastases had a significantly better survival than did those with metastases at other sites (50% vs 0% at 5 years). Laparoscopic cytoreductive nephrectomy has also been performed successfully in preparation for immunotherapy with the potential benefit of less morbidity and faster recovery. In a small pilot study, time to initiation of IL-2 immunotherapy was only 37 days after laparoscopic tumor morcellation.[26] However, further randomized trials are needed to confirm the true benefit of laparoscopic nephrectomy. **Prospective Studies**

We now have information from randomized controlled trials suggesting that cytoreductive surgery followed by immunotherapy improved time to progression and median survival in patients with metastatic renal cell carcinoma (Table 1).[8,9]

- **EORTC 30947**-In a trial conducted by the European Organization for Research and Treatment of Cancer (EORTC 30947),[9] 85 patients were randomized to either radical nephrectomy followed by interferon-alpha or interferon-alpha alone at $5 * 10^6$ IU/m^2 three times per week. Treatment was stratified according to World Health Organization (WHO) performance status 0 to 1, the presence of lung metastases, and unresectable measurable or evaluable disease. Patients with infradiaphragmatic caval and renal vein thrombus who otherwise were eligible to undergo surgery also qualified for entry into the trial. A clear advantage existed in terms of time to progression (5 vs 3 months, hazard ratio = 0.60, 95% confidence interval [CI] = 0.36-0.97) and median survival (17 vs 7 months, hazard ratio = 0.54, 95% CI = 0.31-0.94) favoring the nephrectomy group. No perioperative deaths occurred; five patients achieved a complete response to combined treatment, and one to interferon-alpha alone. However, at 3 years, only 15% of patients were alive in both the control and the nephrectomy groups.
- **SWOG 8949**-In the larger trial by the Southwest Oncology Group (SWOG 8949),[8] 241 patients with metastatic renal cell carcinoma were randomized to nephrectomy followed by interferon-alpha vs interferon alone at $5 * 10^6$ IU/m three times per week. The eligibility criteria and stratification were nearly identical to those of the EORTC trial. An advantage was found in terms of median survival (8.1 vs 11.1 months) favoring the nephrectomy arm (P = .05). The survival advantage in the nephrectomy arm existed across all stratification groups, ie, in patients with performance status 0 (11.7 vs 17.4 months), performance status 1 (4.8 vs 6.9 months), measurable disease (7.8 vs 10.3 months), nonmeasurable disease (11.2 vs 16.4 months), and either lung metastases (10.3 vs 14.3 months) or other sites of metastases (6.3 vs 10.2 months). One operative death occurred (< 1%). Three patients in both groups achieved objective responses. It is noteworthy that both trials only included patients with good performance status (WHO or SWOG performance status 0 or 1), and in SWOG 8949, patients with metastatic disease other than lung also appeared to benefit.

Conclusions From retrospective and prospective studies, it has become clear that cytoreductive surgery followed by immunotherapy in a selected group of patients with good performance status is highly beneficial and should be viewed as the standard of care for such patients. However, such treatment should not be considered a standard for all patients presenting with metastatic disease, as it may adversely affect outcome in the short term for patients with poor performance status. With modern surgical techniques, cytoreductive surgery is a safe procedure with acceptable mortality and morbidity. In our view, cytoreductive surgery followed by immunotherapy should be the standard arm for future clinical trials in patients with metastatic renal cell carcinoma presenting with good performance status.

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