

Sarcomatoid Renal Cell Carcinoma: Biologic Behavior, Prognosis, and Response to Combined Surgical Resection and Immunotherapy

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Purpose: Sarcomatoid variants of renal cell carcinoma (RCC) are aggressive tumors that respond poorly to immunotherapy. We report the outcomes of 31 patients with sarcomatoid RCC treated with a combination of surgical resection and immunotherapy.

Patients and Methods: Patients were identified from the database of the University of California Los Angeles Kidney Cancer Program. We retrospectively reviewed the cases of 31 consecutive patients in whom sarcomatoid RCC was diagnosed between 1990 and 1997. Clinical stage, sites of metastasis, pathologic stage, and type of immunotherapy were abstracted from the medical records. The primary end point analyzed was overall survival, and a multivariate analysis was performed to distinguish any factors conferring an improved survivorship.

Results: Twenty-six percent of patients were male and 74% were female, and the median age was 59 years (range, 34 to 73 years). Length of follow-up ranged from 2 to 77 months (mean, 21.4 months). Twenty-eight patients (84%) had known metastases at the time of radical nephrectomy (67% had lung metastases and 40% had bone, 21% had liver, 33% had lymphatic, and 15% had brain metastases). Twenty-five patients (81%) received immunotherapy, including low-dose interleukin (IL)-2-based therapy (five patients), tumor-infiltrating lymphocyte-based therapy plus IL-2

(nine patients), high-dose IL-2-based therapy (nine patients), dendritic cell vaccine-based therapy (one patient), and interferon alpha-based therapy alone (one patient). Two patients (6%) achieved complete responses (median duration, 46+ months) and five patients (15%) achieved partial responses (median duration, 36 months). One- and 2-year overall survival rates were 48% and 37%, respectively. Using a multivariate analysis, age, sex, and percentage of sarcomatoid tumor (< or > 50%) did not significantly correlate with survival. Improved survival was found in patients receiving high-dose IL-2 therapy compared with patients treated with surgery alone or any other form of immunotherapy ($P = .025$). Adjusting for age, sex, and percentage of sarcomatoid tumor, the relative risk of death was 10.4 times higher in patients not receiving high-dose IL-2 therapy. Final pathologic T stage did not correlate significantly with outcome, but node-positive patients had a higher death rate per year of follow-up than did the rest of the population (1.26 v 0.76, Cox regression analysis).

Conclusion: Surgical resection and high-dose IL-2-based immunotherapy may play a role in the treatment of sarcomatoid RCCs in select patients.

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IT IS ESTIMATED THAT renal cell carcinoma (RCC) will be diagnosed in 29,900 patients in 1998 and that 11,000 of these patients will die from the disease.¹ The incidence has been gradually increasing, with the increased availability of ultrasound and computed tomography (CT), and more of these lesions are diagnosed incidentally.²⁻⁴ Sarcomatoid RCC was first described by Farrow et al⁵ in 1968. It is a distinct pathologic variant of RCC, defined histologically by the highly pleomorphic spindle cells and/or giant cells resembling sarcoma, along with a varying degree of clear or granular epithelial cells that typify RCC. It is an uncommon renal malignancy, with a reported incidence of 0.7% to 13.2% of all renal parenchymal carcinomas.⁵⁻¹¹ Clinically, sarcomatoid RCC is locally aggressive and potentially metastatic and is associated with poor prognosis.^{5-8,12-14} Surgical resection alone does not seem to affect the clinical course significantly, because these tumors are usually metastatic or locally advanced at the time of diagnosis.

Controversy exists regarding the responsiveness of sarcomatoid RCC to chemotherapy and immunotherapy.^{7,9,15}

Patients who are unresponsive to chemotherapy or immunotherapy have an overall poor survival. In the mid 1980s, the use of high-dose interleukin (IL)-2 in the treatment of metastatic RCC was introduced and an objective response rate of 14% in patients with metastatic RCC was observed.¹² At the University of California Los Angeles (UCLA), we have also observed encouraging results in similar patients with IL-2-based immunotherapy.^{16,17} Our current approach includes surgical resection of the primary tumors in combination with immunotherapy. Given the uncommon nature of the sarcomatoid RCC and the failure of a traditional

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approach in these patients, we investigated the efficacy of surgical resection and immunotherapy in combination as treatment for sarcomatoid RCC.

PATIENTS AND METHODS

Patients

We retrospectively analyzed cases of 31 consecutive patients from the UCLA Kidney Cancer Program, in which more than 1,000 patients have participated. A diagnosis of sarcomatoid variant was made between 1990 and 1997 in all patients. Clinical stage, site of metastases, pathologic stage, and type of immunotherapy were abstracted from the medical records. All 31 patients underwent aggressive surgical management and 25 (80.7%) received postoperative adjuvant immunotherapy. Six patients (19.4%) were treated with surgery alone and one patient had a partial nephrectomy.

Surgical Technique

Radical nephrectomy was performed by one of two surgeons. Each patient underwent removal of Gerota's fascia and adrenal and a regional lymphadenectomy. In patients with single metastases, metastectomy was performed. If a patient had a renal vein or inferior vena cava tumor thrombus, this was resected en bloc. If tumor-infiltrating lymphocytes (TILs) were used, these were cultured in a sterile manner from the resected specimen.

Pathology

All specimens were inked, placed in formalin, and sectioned according to the usual protocol. Sarcomatoid variant was diagnosed by a staff pathologist when any portion of the kidney displayed features consistent with sarcoma-appearing spindle cells. The percentage of sarcomatoid tumor varied among specimens, which were grossly characterized as less than or greater than 50% sarcomatoid variant. Under high power, the nuclei had a typical appearance of spindle-shaped cells with pleomorphic nuclei. In all specimens, epithelial elements were confirmed and were granular, clear cell, or both. Staging was performed using the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system.¹⁸ Nuclear grading with light microscopy was performed according to Fuhrman et al.¹⁹

Immunotherapy

Patients who received immunotherapy received high- or low-dose IL-2-based immunotherapy or TIL-based therapy. No patients received TIL and high-dose IL-2 combination therapy. Immunotherapy was usually begun 4 to 8 weeks after surgical resection. The UCLA protocol for high-dose IL-2 therapy involved administration of an intravenous bolus (600,000 IU/kg) of recombinant IL-2 (package insert, Proleukin, Chiron Therapeutics, Emeryville, CA) every 8 hours up to 14 times. After a 9-day rest interval, the same cycle was repeated. Cardiac, pulmonary, renal, and other adverse side effects were monitored throughout the period of therapy and thereafter. Therapy was administered in a monitored hospital room. Restaging was carried out at 6 weeks, and if a response was noted, an identical course was repeated.

Low-dose IL-2 therapy involved administration of IL-2 72,000 IU/kg every 8 hours, up to 14 doses.²⁰ After a 9-day rest interval, a second 14-dose course was administered. The UCLA protocol for low-dose subcutaneous IL-2 therapy involved administration of 18×10^6 IU of IL-2 for 4 weeks with 2-week rest intervals. In continuous-infusion

low-dose IL-2 therapy, 6×10^6 IU/m²/d was given for 4 days, followed by a 3-day rest interval.^{21,22}

Interferon alfa (IFN α) was given by subcutaneous injection during low-dose continuous-infusion IL-2 therapy. The dose regimen was 6×10^6 IU/m²/d on days 1 and 4 of each treatment week of low-dose IL-2 therapy.^{23,24} Tumor-infiltrating lymphocytes were harvested from the primary tumor, expanded ex vivo in the presence of IL-2, and then reinfused along with IL-2. If patients were candidates, "cytokine priming" of the regimen just discussed with IFN α and IL-2 was performed.¹⁶ Dendritic cell vaccine-based therapy was performed using a vaccine of dendritic cells cultured from the patients.²⁵

Patient Follow-Up and Response

Patients were followed up in the UCLA Kidney Cancer Program at 3- to 6-month intervals. Interval follow-up involved a detailed history, physical examination, complete blood count, electrolyte panel, liver function tests, determination of calcium and alkaline phosphatase levels, and imaging studies (abdominal CT scan, chest CT scan, and, when applicable, head CT scan). Complete response (CR) was defined as complete disappearance of clinically measurable disease for a minimum of 4 weeks. Partial response was defined as 50% reduction of tumor volume, as measured by the sum of the products of the two longest perpendicular diameters, for at least 4 weeks with no simultaneous progression of measurable disease nor appearance of new lesions. Stable disease was defined as a less than 25% increase or less than 50% decrease in tumor size without progression of measurable disease or the appearance of new lesions. Patients were evaluated for response after each 6-week course of treatment. Response duration was calculated from the date of the initial response to the most recent evaluation or to the point of documented progression.

Survival was calculated from the time of diagnosis to the date of last follow-up or to the time of death. Duration of response was calculated for responding patients only and was defined as the interval from the date of response to disease progression or to the date of last follow-up. Survivorship analysis was performed using Kaplan-Meier survivorship curves with log-rank tests for comparing groups, and multivariate survivorship analysis was performed using the Cox proportional hazards model.

RESULTS

Patient Characteristics

The mean age of the patients was 55.3 years (range, 34 to 73 years). Eight patients were female and 23 were male. The tumor stages ranged from T1 to T4N+. In one patient (3.2%) the tumor stage was T1, in two patients (6.7%) it was T2, in 19 patients (61.3%) it was stage T3, and in eight patients (25.8%) it was T4 (Fig 1). Seven patients (22.6%) had regional lymph node involvement. The primary tumor sizes ranged from 3 to 18 cm (mean, 8.6 cm). Twenty-six patients (84%) had known metastases at the time of radical nephrectomy. Twenty-two (71%) of 31 patients had lung metastases, 13 (44%) had bone metastases, five (16%) had brain metastases, and seven (23%) had liver metastases (Fig 2). Eastern Cooperative Oncology Group performance status of the patients receiving immunotherapy was 0 to 1.

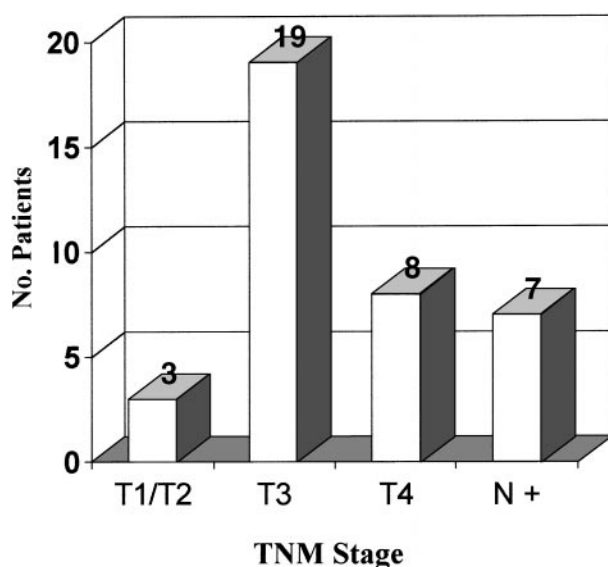


Fig 1. Distribution of tumor-node-metastasis stages among patients with sarcomatoid tumors.

Surgery

Thirty (97%) of 31 patients had radical nephrectomies and one patient (3%) with a horseshoe kidney had a partial nephrectomy. One patient had a liver resection and two patients had diaphragmatic resections. One patient had a bowel resection and one patient had a pancreas resection. Nine patients (29%) had renal vein and vena cava involvement. Postoperative ileus occurred in two patients. There were no other surgical complications. The mean estimated blood loss was 1,400 cm³ (range, 200 to 4,500 cm³). Twelve patients had a less than 50% sarcomatoid variant in the specimen, whereas 19 had a greater than 50% sarcomatoid tumor in the specimen.

Immunotherapy

Immunotherapy was given to 25 (81%) of 31 patients. Several groups were substratified based on the type of immunotherapy given (Fig 3). Nine patients (36%) had high-dose IL-2 immunotherapy and nine patients were treated with a combination of TILs, IFN α , and low-dose IL-2. Fourteen patients (56%) had low-dose IL-2 therapy (alone or in combination) and five patients (20%) were treated with low-dose IL-2 alone. One patient (4%) was treated with interferon alpha-based therapy alone and one patient (4%) had dendritic cell vaccine-based therapy. The number of cycles ranged from one to three (average, two cycles).

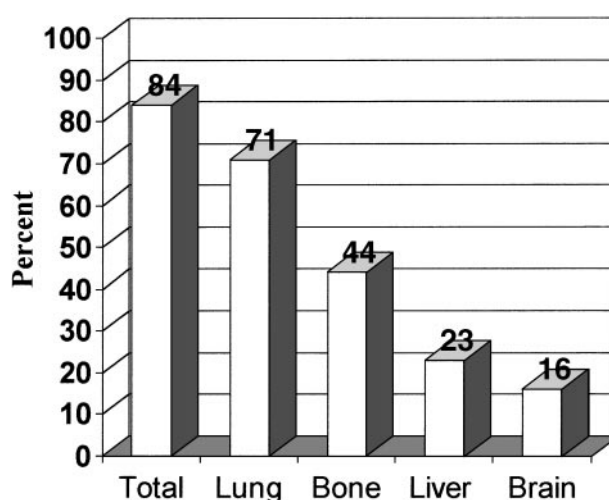


Fig 2. Sites of distant metastases and percentages of patients with metastases at these sites.

Immunotherapy Toxicity

Complications during or after immunotherapy occurred in 18 patients (72%). Seven patients (18%) along with four (44%) of the nine patients treated with high-dose IL-2 experienced no complications. Complications included anorexia, dyspnea, fatigue, low-grade fever, hypotension, mental status changes, lower extremity edema, temporarily elevated serum creatinine level, dysrhythmia, anemia, hyperkalemia, and hypoadosteronism. The most frequently expe-

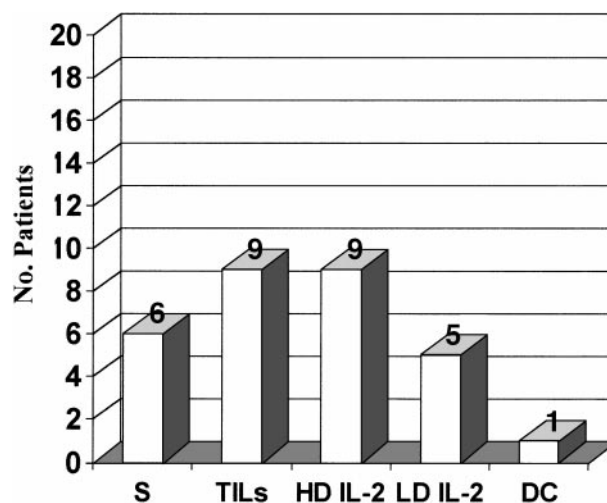


Fig 3. Type of treatment. S, surgery alone; TILs, combination therapy (IFN α , TILs, and low-dose IL-2); HD IL-2, high-dose IL-2 therapy; LD IL-2, treatment with low-dose IL-2 alone; DC, dendritic cell vaccine-based therapy.

rienced complication was dyspnea, which occurred in four patients (16%). No patient had a severe side effect or died from immunotherapy-related complications.

Treatment Response and Survival

All survival data were calculated from the time of surgery. Length of follow-up for all survivors ranged from 2 to 77 months (mean, 16.5 months; median, 6.5 months). Overall survival for the entire study group at 1 and 2 years was 48% and 37%, respectively (Fig 4). Seventeen (55%) of the 31 patients died. Using a multivariate analysis, only two variables were significantly related to risk of death after adjusting for age, sex, and less than 50% sarcomatoid tumor: no high-dose IL-2 therapy ($P = .025$) and tumor stage ($P = .014$). The median length of survival of patients not receiving high-dose IL-2 therapy was 6 months. Only one of nine patients receiving high-dose IL-2 therapy died, but one was lost to follow-up and presumed dead at 17 months (Fig 5). The median survival of the patients receiving high-dose IL-2 therapy had not been reached with a median follow-up of 10.4 months (range, 2 to 77 months; mean, 21.4 months). The survivorship curves are presented in Fig 6. The relative risk of death adjusted for age, sex, and less than 50% sarcomatoid variant for patients not receiving any IL-2 was 10.4 times higher than for patients receiving IL-2.

Overall, two patients (6%) achieved a CR, with a duration of 46+ and 65+ months (Table 1). One of the patients was treated with surgery alone and the other with the combination of IFN α , TILs, and low-dose IL-2. Five patients (15%) achieved a partial response, with a median duration of 36+ months. The survival and response data are summarized in Table 1. Final pathologic T stage did not correlate significantly with outcome, but node-positive patients showed a higher death rate per year of follow-up compared with the

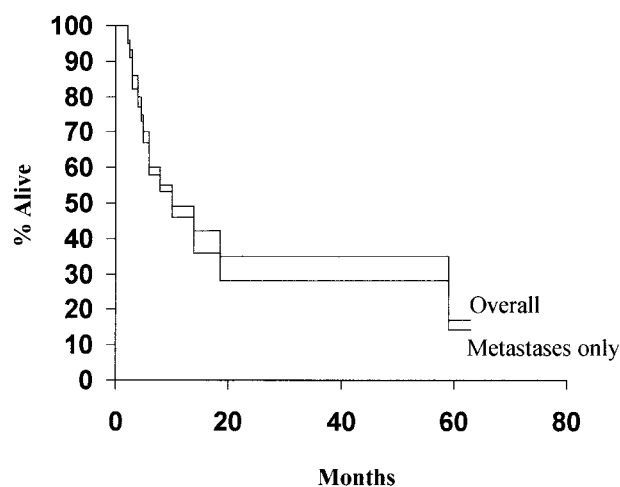


Fig 4. Overall survival of all patients and those with metastases.

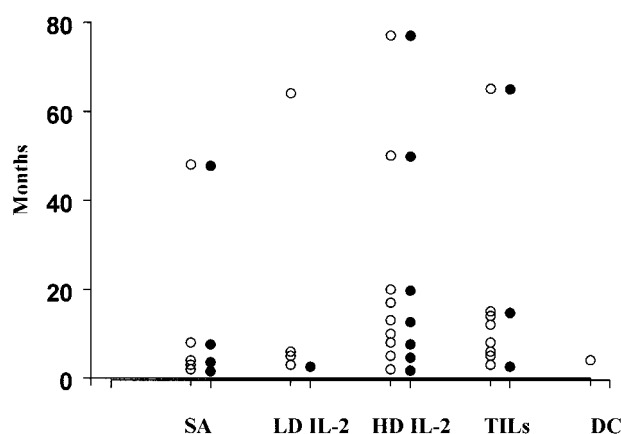


Fig 5. Scattergram of length of follow-up (from time of surgery to last follow-up or death) for population (○) and survivors (●) among patients treated with immunotherapy (n = 31). SA, surgery alone; LD IL-2, low-dose IL-2 therapy; HD IL-2, high-dose IL-2 therapy; TILs, combination therapy (IFN α , TILs, and low-dose IL-2); DC, dendritic cell vaccine-based therapy.

rest of the population (1.26 v 0.76, $P = .09$; Cox regression analysis) (Fig 7). There was no significant correlation between survival and age, sex, and percentage of sarcomatoid tumor (< or > 50%).

DISCUSSION

Sarcomatoid RCC is a biphasic lesion with both mesenchymal (sarcomatous) and epithelial (carcinoma) elements.^{5,13} It has been found to have an increased proliferative activity and is locally aggressive, has high metastatic potential, and is associated with poor prognosis.^{8,14} In patients with the disease, reported median survival durations from the time of diagnosis are 3.8 to 6.8 months when no treatment is given.^{5,7,12} Surgical resection alone does not change the

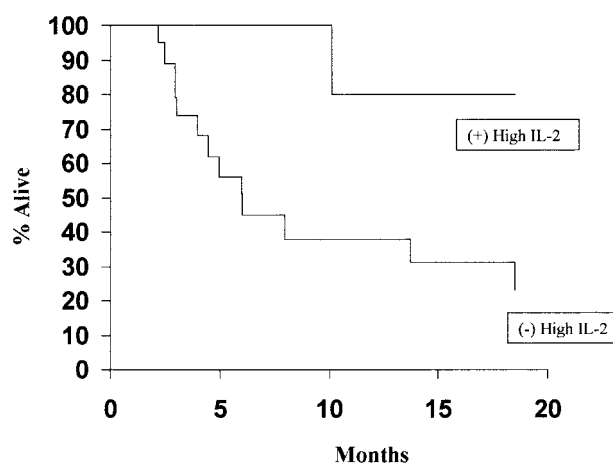


Fig 6. Kaplan-Meier survivorship curve of patients with sarcomatoid RCC treated with high-dose IL-2 therapy and either surgery alone or any other form of immunotherapy ($P = .0175$).

Table 1. Distribution of Responses Based on Type of Immunotherapy

Treatment	No. of Patients	Survival (months)		% Response			
		Median	Range	CR	PR	PD	D
Surgery alone	6	5	3-64	17	17	33	33
High-dose IL-2 therapy	9	nr*	2-77	0	22	56	22
Low-dose IL-2 therapy	5	3	2-48	0	0	40	60
Combination therapy (IFN α , TILs, and low-dose IL-2)	9	8	3-65	11	22	22	67
Dendritic cell vaccine-based therapy	1	4		0	0	0	100

Abbreviations: PR, partial response; PD, progressive disease; D, death.

*Not reached with a median length of follow-up of 10.4 months.

prognosis of these patients. The pathologic stage has been shown to be the best single prognostic factor in patients with RCC and has been found to be equally important in patients with sarcomatoid RCC. Ro et al¹² found two factors to independently predict poorer prognosis—tumor necrosis (moderate to massive) and the proportion of sarcomatoid tumor (but only if the tumor was stage I or II. When stratified by T stage, patients with sarcomatoid RCC were found to have mean survival durations of 49.7 months (T1) and 6.8 months (T2 to T4).^{12,26} Lymph node-positive disease, distant metastases, and capsular invasion affected prognosis but not renal vein or inferior vena cava involvement. On the other hand, Bertoni et al²⁷ found that the percentage of sarcomatoid involvement did not seem to be important for prognosis unless it was less than 5%. The patients with less than 5% sarcomatoid RCC in the specimen had better prognoses. Patient age, female sex, and evidence of distant metastases were significantly associated with poor prognosis, but mitotic count, degree of pleomorphism, cellularity, and amount of matrix in the sarcomatoid areas did not correlate with prognosis.¹²

The response of RCC to chemotherapy and immunotherapy has been controversial. Sella et al⁷ studied patients who were treated with various chemotherapeutic agents and/or immunotherapeutic agents and found a longer median survival duration in treated patients than in patients who were not treated (13.8 months v 3.8 months). Two (25%) of eight patients treated with doxorubicin-based chemotherapy showed CR with follow-up of 50 and 65 months. There was no statistically significant advantage to any regimen, although the patients treated with IFN α had the longest median survival duration (41 months). On the other hand, the benefit of IFN α therapy was not confirmed in a study by Culine et al.⁹ In their study, none of the four patients treated with IFN α responded, but three patients who responded to doxorubicin-based chemotherapy survived longer than those who did not respond. Although the significance of this small series of patients is unclear, it set

the stage for our study in today's era of immune modulation in sarcomatoid RCC.

Recombinant IL-2 is currently the only agent approved by the United States Food and Drug Administration for treatment of metastatic RCC. IL-2 induces production of various cytokines from lymphocytes in vivo and stimulates T-cell growth in vivo.²⁸ High-dose IL-2 therapy has produced an objective response rate of 15% to 20%, with occasional long-term durable remissions.^{16,29,30} The duration of responses are impressive, with a median duration of 20 months among responders.²² Other cytokines such as IFN α and interferon gamma, alone and in combination with IL-2, have also been used, and newer therapeutic approaches, including the use of TILs incubated and expanded ex vivo with IL-2, have been developed to increase the efficacy of high-dose IL-2 therapy. Overall response rates have been found to be greater than 34% and CR rates have been found to be as high as 9.1% in patients treated with IFN α priming before aggressive surgical management, low-dose IL-2, and ex vivo expansion of TILs.¹⁶

In our study, patients with a diagnosis of sarcomatoid RCC who were treated with aggressive surgical resection and high-dose IL-2 therapy had a significantly improved survival compared with patients treated with any other form of immunotherapy or with surgery alone. The disease progressed in more than half of the patients, as observed through long-term follow-up. There was a clear suggestion that stage is related to risk of death, but because of the small number of patients with low (T1 or T2) or N+ tumor stages, statistical significance was not reached ($P = .089$). We did not

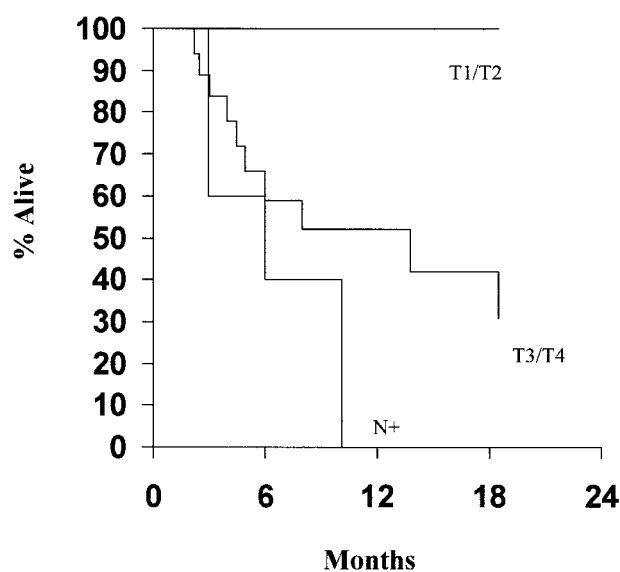


Fig 7. Kaplan-Meier survivorship curve of patients with sarcomatoid RCC stratified by tumor-node-metastasis stage (all patients had metastases) ($P = .089$).

find the percentage of sarcomatoid tumor, age, and sex to be independent predictors of survival. A meaningful analysis of all patients treated with immunotherapy versus surgery alone was difficult because the number of patients undergoing surgery alone was small. Only one patient in the group of patients undergoing surgery alone had a prolonged survival (48+ months) free of measurable disease. The adjusted relative risk of death for patients not receiving IL-2 therapy was 10.4 times higher than for those treated with surgery alone or with any other form of immunotherapy. The data indicate that select patients (good performance status) with sarcomatoid RCC should be considered for treatment with aggressive surgical management and IL-2-based immunotherapy.

In conclusion, we have described the largest reported experience of patients with sarcomatoid RCC treated with immunotherapy. We found that patients who underwent aggressive surgical resection alone had poor overall survival compared with patients who were treated with aggressive surgical resection and adjunctive immunotherapy. Patients with sarcomatoid RCC treated with the combination of aggressive surgical resection and high-dose IL-2 had a survival advantage. Our results suggest that even with the most aggressive sarcomatoid tumors, the combination of aggressive surgical therapy and IL-2-based immunotherapy confers a survival advantage in select patients. Further study is needed to confirm these findings.

REFERENCES

1. Landis S, Murray T, Bolden S, et al: Cancer statistics, 1998. *CA Cancer J Clin* 48:1-29, 1998
2. Belldegrun A, Abi-Aad A, Figlin R, et al: Renal cell carcinoma: Basic biology and current approaches to therapy. *Semin Oncol* 18:96-101, 1991 (suppl 7)
3. Mulders P, Figlin R, deKernion J, et al: Renal cell carcinoma: Recent progress and future directions. *Cancer Res* 57:5189-5195, 1997
4. Franklin JR, Figlin R, Belldegrun A: Renal cell carcinoma: Basic biology and clinical behavior. *Semin Urol Oncol* 14:208-215, 1996
5. Farrow GM, Harrison EG Jr, Utz DC: Sarcomas and sarcomatoid and mixed malignant tumors of the kidney in adults: 3. *Cancer* 22:556-563, 1968
6. Tomera KM, Farrow GM, Lieber MM: Sarcomatoid renal carcinoma. *J Urol* 130:657-659, 1983
7. Sella A, Logothetis C, Ro J, et al: Sarcomatoid renal cell carcinoma: A treatable entity. *Cancer* 60:1313-1318, 1987
8. Oda H, Machinami R: Sarcomatoid renal cell carcinoma: A study of its proliferative activity. *Cancer* 71:2292-2298, 1993
9. Culine S, Bekradda M, Terrier-Lacombe M, et al: Treatment of sarcomatoid renal cell carcinoma: Is there a role for chemotherapy? *Eur Urol* 27:138-141, 1995
10. Skinner DG, Colvin RB, Vermillion CD, et al: Diagnosis and management of renal cell carcinoma: A clinical and pathologic study of 309 cases. *Cancer* 28:1165-1177, 1971
11. Bennington J: Proceedings: Cancer of the kidney—Etiology, epidemiology, and pathology. *Cancer* 32:1017-1029, 1973
12. Ro JY, Ayala AG, Sella A, et al: Sarcomatoid renal cell carcinoma: Clinicopathologic. A study of 42 cases. *Cancer* 59:516-526, 1987
13. Bonsib SM, Fischer J, Plattner S, et al: Sarcomatoid renal tumors: Clinicopathologic correlation of three cases. *Cancer* 59:527-532, 1987
14. Juhasz J, Sebok J, Galambos J, et al: Renal carcinosarcoma (mixed tumours) of the kidney. *Int Urol Nephrol* 122:103-108, 1980
15. Lopera H, Theodore C, Ghosn M, et al: Phase II trial of combination chemotherapy with dacarbazine, cyclophosphamide, cisplatin, doxorubicin, and vindesine (DECAV) in advanced renal cell cancer. *Urology* 34:5:281-283, 1989
16. Figlin RA, Pierce WC, Kaboo R, et al: Treatment of metastatic renal cell carcinoma with nephrectomy, interleukin-2 and cytokine-primed or CD8(+) selected tumor infiltrating lymphocytes from primary tumor. *J Urol* 158:740-745, 1997 (part 1)
17. Franklin JR, Figlin R, Rauch J, et al: Cytoreductive surgery in the management of metastatic renal cell carcinoma: The UCLA experience. *Semin Urol Oncol* 14:230-236, 1996
18. American Joint Committee on Cancer: Manual for Staging of Cancer (ed 5). Philadelphia, PA, Lippincott-Raven, 1997, pp 231-232
19. Furhman SA, Lasky LC, Limas C: Prognostic significance of morphologic parameters in renal cell carcinoma. *Am J Surg Pathol* 6:655-663, 1982
20. Yang JC, Topalian SL, Parkinson D, et al: Randomized comparison of high-dose and low-dose intravenous interleukin-2 for the therapy of metastatic renal cell carcinoma: An interim report. *J Clin Oncol* 12:1572-1576, 1994
21. Taneja SS, Pierce W, Figlin R, et al: Immunotherapy for renal cell carcinoma: The era of interleukin-2-based treatment. *Urology* 45:911-924, 1995
22. Taneja SS, Pierce W, Figlin R, et al: Management of disseminated kidney cancer. *Urol Clin North Am* 214:625-637, 1994
23. Figlin RA, Belldegrun A, Moldawer N, et al: Concomitant administration of recombinant human interleukin-2 and recombinant interferon- α 2A: An active outpatient regimen in metastatic renal cell carcinoma. *J Clin Oncol* 10:414-421, 1992
24. Vogelzang NJ, Lipton A, Figlin RA: Subcutaneous interleukin-2 plus interferon α -2a in metastatic renal cancer: An outpatient multicenter trial. *J Clin Oncol* 11:1809-1816, 1993
25. Hinckel A, Gitlitz B, Mulders P, et al: Dendritic cell (DC) therapy for metastatic renal cell cancer (MRCC): From basic research to a phase I clinical trial. 1998 Annual meeting of the American Urological Association, San Diego, CA. *J Urol* 159:148, 1998 (suppl)
26. Selli C, Hinshaw W, Woodard, B, et al: Stratification of risk factors in renal cell carcinoma. *Cancer* 52:899-903, 1983
27. Bertoni F, Ferri C, Benati A, et al: Sarcomatoid carcinoma of the kidney. *J Urol* 137:25-28, 1987
28. Belldegrun A, Tso C, Kaboo R, et al: Natural immune reactivity—associated therapeutic response in patients with metastatic renal cell carcinoma receiving tumor-infiltrating lymphocytes and interleukin-2-based therapy. *J Immunol Emphasis Tumor Immunol* 192:149-161, 1996
29. Lotze MT, Chang AE, Seipp CA, et al: High-dose recombinant interleukin 2 in the treatment of patients with disseminated cancer: Responses, treatment-related morbidity, and histologic findings. *JAMA* 256:3117-3124, 1986
30. Fyfe G, Fisher R, Rosenberg S, et al: Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol* 13:688-696, 1995