# Survival and Prognostic Stratification of 670 Patients With Advanced Renal Cell Carcinoma

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***Purpose:*** **To identify prognostic factors and a model predictive for survival in patients with metastatic renal-cell carcinoma (RCC).**

***Patients and Methods:*** **The relationship between pretreatment clinical features and survival was studied in 670 patients with advanced RCC treated in 24 Memorial Sloan-Kettering Cancer Center clinical trials between 1975 and 1996. Clinical features were first examined univariately. A stepwise modeling approach based on Cox proportional hazards regression was then used to form a multivariate model. The predictive performance of the model was internally validated through a two-step nonparametric bootstrapping process.**

***Results:*** **The median survival time was 10 months (95% confidence interval [CI], 9 to 11 months). Fifty-seven of 670 patients remain alive, and the median follow-up time for survivors was 33 months. Pretreatment features associated with a shorter survival in the multivariate analysis were low Karnofsky performance status (<80%), high serum lactate dehydrogenase (> 1.5 times upper limit of normal), low hemoglobin (< lower limit of normal), high ''corrected'' serum calcium (> 10 mg/dL), and absence of prior nephrectomy. These were used as risk factors to categorize patients into three different groups. The median time to death in the 25% of patients with zero risk factors (favorable-risk) was 20 months. Fifty-three percent of the patients had one or two risk factors (intermediate-risk), and the median survival time in this group was 10 months. Patients with three or more risk factors (poor-risk), who comprised 22% of the patients, had a median survival time of 4 months.**

***Conclusions:*** **Five prognostic factors for predicting survival were identified and used to categorize patients with metastatic RCC into three risk groups, for which the median survival times were separated by 6 months or more. These risk categories can be used in clinical trial design and interpretation and in patient management. The low long-term survival rate emphasizes the priority of clinical investigation to identify more effective therapy.**

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RENAL CELL CARCINOMA (RCC) is the most common tumor arising in the kidney, affecting approximately 30,000 individuals each year in the United States.[1,2] The outlook for patients with distant metastases is poor, with a 5-year survival rate of less than 10% for patients presenting with stage IV disease.[1,2] This reflects the lack of effective systemic therapy for patients with metastases. RCC is resistant to chemotherapy and hormonal therapy because no agent consistently achieves a response in more than 10% of patients.[3] Immunotherapy, ie, interleukin-2 and interferon alpha, achieves responses in 10% to 20% of patients.[1] However, the low response rate, toxicity associated with high-dose regimens,[4] and few long-term survivors after treatment with interferon-alpha or interleukin-2 provide the rationale for clinical trials as a priority for management of patients with this disease.

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Determining prognostic factors of survival for patients with advanced RCC would be valuable in directing therapy and interpreting results of clinical trials. Clinical trials in RCC frequently use biologic agents where responses may be delayed for 3 months or more after the institution of therapy,[5] and prospective assessment of patient survival is necessary to determine appropriate eligibility. Response proportions to interferon-alpha, interleukin-2, or combination programs vary considerably among phase II trials,[6] implying patient selection is an important factor in achieving a favorable treatment outcome. Clinical trials that include survival as an end point must account for prognostic factors to assure that treatment groups are comparable so that the proper interpretation of trial outcome can be ascertained. Also, an assessment of patient survival benefits both patient and physician in clinical management.

Published analyses of prognostic factors performed in a multivariate analysis have been limited in both the number of series and the number of patients studied.[7-12] To define pretreatment features predictive of survival, we performed a retrospective study on 670 patients with advanced RCC treated in successive clinical trials at the Memorial Sloan-Kettering Cancer Center (MSKCC). The results were examined by multivariate analysis, and a model was developed to stratify patients according to risk.

## PATIENTS AND METHODS

### *Patients*

All patients were treated on MSKCC Institutional Review Board–approved clinical trials conducted between September 1975 and July 1996. The patients were identified through registration on 24 consecutive MSKCC clinical trials; the specific eligibility and treatment programs have previously been described (Table 1).[13-33] Eligibility details are described in individual reports but all included histologic confirmation of RCC, stage IV disease with presence of measurable lesions, adequate Karnofsky performance status, lack of severe comorbid conditions, and adequate hematologic, renal, and hepatic function.

Patients entered onto more than one clinical trial were evaluated for this study at the time of entry on their first MSKCC trial. Routine studies at the time of clinical trial entry included the following: detailed history and physical examination, complete blood count, prothrombin and partial thromboplastin times, creatinine, total bilirubin, alkaline phosphatase, AST lactate dehydrogenase, blood urea nitrogen, calcium, total protein, albumin, and imaging studies to assess measurable disease. The majority of patients had a computerized tomography scan of the abdomen and chest to assess extent of disease. Response to treatment, time to progression after systemic therapy, and survival and current status were recorded.

**Table 1. Composition of MSKCC Retrospective Study**

| Protocol Reference | Agent(s) | No. of Patients | Accrual Dates |
|---|---|---|---|
| 14 | Vindesine | 18 | 9/75-5/77 |
| 15 | Methyl GAG | 29 | 11/79-5/80 |
| 16 | Flutamide | 23 | 6/80-2/82 |
| 17 | 4-epi-doxorubicin | 10 | 7/80-9/81 |
| 18 | 10-deaza-aminopterin | 12 | 7/80-7/83 |
| * | AAFC* | 2 | 2/81-5/81 |
| 19 | Bisantrene | 18 | 5/81-10/81 |
| 20 | 4-demethoxydaunorubicin | 17 | 2/82-10/82 |
| 13 | Interferon-α | 36 | 3/82-4/83 |
| 13 | Interferon-α | 58 | 7/83-5/84 |
| 22 | Elliptinium | 9 | 9/83-1/84 |
| 21 | *N*-methyl-formamide | 14 | 4/84-4/85 |
| 13 | Interferon-α +/− vinblastine | 51 | 6/84-3/86 |
| 23 | Trimetrexate | 14 | 9/86-9/87 |
| 24 | Interleukin-2 | 68 | 9/87-3/89 |
| 26 | Didemnin | 20 | 2/88-9/89 |
| 27 | Interleukin-2 plus interferon-α | 34 | 7/89-8/90 |
| 28 | Suramin | 21 | 8/90-6/91 |
| 29 | Vinblastine | 23 | 6/91-10/93 |
| 30 | Topotecan | 15 | 12/91-6/92 |
| 31 | Liposomal doxorubicin | 11 | 9/92-2/94 |
| 25 | Interferon-α plus 13-cis-retinoic acid | 40 | 1/93-4/94 |
| 32† | Interferon-α +/− 13-cis-retinoic acid | 109 | 4/94-7/96 |
| 33 | 13-cis-retinoic acid | 18 | 6/94-2/95 |

Abbreviations: AAFC, 2′2-anhydro-1-B-D-arabino-F-fluorocytosine; Methyl GAG, methylglyoxal bis(guanylhydrazone)dihydrochloride.

*Trial unpublished.

†Only patients treated at MSKCC included; patients treated by Eastern Cooperative Oncology Group were used as an external validation set and are described in a separate publication.

**Table 2. Patient Characteristics**

| Characteristic | No. of Patients | % | Range |
|---|---|---|---|
| No. of patients | 670 | | |
| Sex | | | |
| Male, % | 450 | 67 | |
| Female, % | 220 | 33 | |
| Age, years | | | |
| Median | 58 | | |
| Range | 18-82 | | |
| Range of diagnosis dates | 6/15/57-6/3/96 | | |
| Karnofsky performance status, % | | | |
| ≤ 60 | 46 | 7 | |
| 70 | 146 | 22 | |
| 80 | 211 | 32 | |
| 90 | 264 | 39 | |
| Prior therapy, % | | | |
| Nephrectomy | 434 | 65 | |
| Radiation therapy | 150 | 22 | |
| Immunotherapy | 56 | 8 | |
| Chemo- or hormonal therapy | 65 | 10 | |
| No. of metastatic sites, % | | | |
| Renal primary or local recurrence only | 19 | 3 | |
| 1 | 242 | 36 | |
| 2 | 253 | 38 | |
| 3 | 110 | 16 | |
| ≥ 4 | 46 | 7 | |
| Sites of metastatic disease, % | | | |
| Lung | 483 | 72 | |
| Mediastinum | 135 | 20 | |
| Retroperitoneal lymph nodes | 134 | 20 | |
| Bone | 176 | 26 | |
| Liver | 130 | 19 | |
| Median baseline laboratory parameters | | | |
| Albumin, normal 4.0-5.7 g/dL | 4 | | 2.3-5.3 |
| Alkaline phosphatase, normal 0-115 U/L | 108 | | 37-1248 |
| Calcium, normal 8.5-10.5 mg/dL | 9.7 | | 6.8-14.6 |
| Corrected calcium, normal < 10 md/dL | 9.3 | | 6.2-14.2 |
| Hemoglobin, normal > 13 g/dL (M); > 11.5 g/dL (F) | 12.3 | | 5.2-18 |
| Lactate dehydrogenase, normal < 200 U/L | 189 | | 59-5380 |

### *Survival Analysis*

The end point of interest was survival time, defined as the time from treatment initiation to the death date or last follow-up date. Clinical features examined included number and sites of metastases (lung, mediastinum, bone, liver, and retroperitoneum), Karnofsky performance status, prior treatment (radiation, chemotherapy, and immunotherapy), prior nephrectomy, the time interval from diagnosis to the start of treatment, and selected baseline biochemical features. The biochemical features were based on a previous analysis and consisted of hemoglobin, serum albumin, alkaline phosphatase, lactate dehydrogenase, and total calcium concentrations.[34] To separate out the effects of

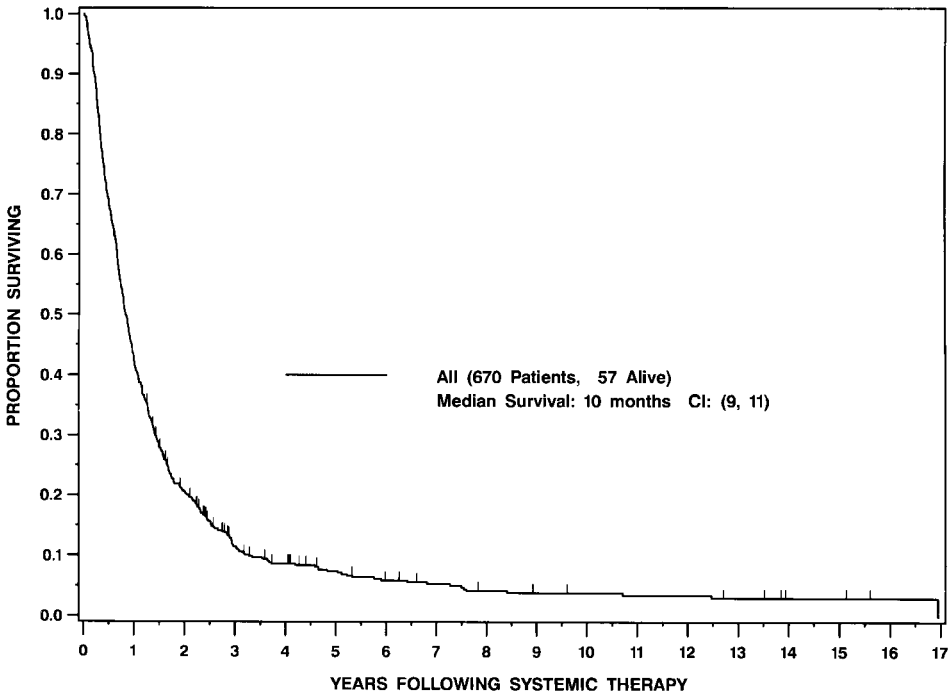


**Fig 1. Overall survival (670 patients, 57 alive). Vertical lines indicate last follow-up.**

protein binding and assess free calcium, an adjustment formula was used: "Corrected" calcium = total calcium − 0.707 [albumin-3.4].[35] The "corrected" calcium value was used in the survival analyses.

Survival distributions were estimated using the Kaplan-Meier method.[36] The relationship between survival and each of the variables was analyzed using the log-rank test[37] for categorical variables and a score test based on Cox proportional hazards regression model[38] for continuous variables. Bivariate relationships among the variables were explored to better understand how the variables interacted and how these interactions related to survival. There were few missing values for any of the variables (no more than 2%), and in all analyses, case deletion was used to handle the missing values. When necessary, a logarithmic transformation was used to reduce skewness.

Two types of exploratory plots were used to display the functional relationship between continuous covariates (eg, lactate dehydrogenase and hemoglobin) and patient survival. The first was the running median survival time plot,[39] which divided the covariate values into overlapping intervals, calculated the Kaplan-Meier–based median survival time for corresponding patients, and plotted these median survival times against the midpoint of the intervals. The second was the predictive failure time plot,[40] which plotted the predicted median survival time based on a Cox regression model against each of the observed covariate values. These two plots are more descriptive of the relationship between a continuous covariate and survival time than a Kaplan-Meier plot. They allow the risk of death to vary according to the value of the covariate instead of assuming that all individuals in one group are at an equivalent risk of death.

### *Multivariate Model*

Using a significant relationship with survival as criteria for including a variable in the stepwise modeling procedure, seven variables were retained and entered into a multivariate model. Because this retrospective study included patients in clinical trials from 1975 through 1996, whose treatment included both cytotoxic therapy and immunotherapy, a stratified Cox proportional hazards model[41] was used to account for differences in the year of treatment and the type of therapy. This model states that the hazard or risk of death at time t for a patient in strata j with variables $x = (x_{1j}, x_{2j}, \ldots, x_{pj})$ is

$$\lambda_j(t,x) = \lambda_{oj}(t) \exp(\beta_1 x_{1j} + \beta_2 x_{2j} + \ldots + \beta_p x_{pj})$$

where $\lambda_{0j}(t)$ is the baseline hazard function for strata j and $\beta_1, \beta_2, \ldots, \beta_p$ are the regression coefficients. According to this model, when the regression coefficient is positive, then the risk of death increases with higher values of the variable. When the regression coefficient is negative, the risk of death decreases with higher values of the variable. Using a stepwise modeling algorithm with a .15 significance level for entering and removing explanatory variables, the independent risk factors were determined and the model was formed.

Because it was desired to dichotomize the continuous variables chosen in the modeling for ease of clinical use, a minimum *P* value approach as well as the above exploratory plots were used to perform a cut point analysis.[42] In the minimum *P* value approach, selected values of the prognostic factor are examined as candidates for the cut point. The value is chosen that best separates patient outcomes according to a maximum $\chi^2$ statistic and minimum *P* value or a maximum relative risk. The *P* value is adjusted to account for the problem of multiple testing. The running median survival time plot and predicted failure time plot were used to restrict a region for the cut point search. Laboratory information about biologic cut points coupled with the information from the statistical techniques guided the decision about which cut point to use for each of the variables. It was verified that the relationship between survival and the prognostic factor remained significant when the variable was dichotomized.

**Table 3. Univariate Survival Analysis of Number and Sites of Metastases and Prior Therapy**

| | % | % Alive | Median Survival | CI | $\chi^2$ | *P* | Risk Ratio |
|---|---|---|---|---|---|---|---|
| Clinical features of metastatic disease | | | | | | | |
| Lung metastases | | | | | | | |
| Yes | 72 | 8 | 9.9 | 8.8-11.0 | 1.79 | .181 | 1.1 |
| No | 28 | 9 | 10.6 | 8.5-13.1 | | | |
| Mediastinum metastases | | | | | | | |
| Yes | 20 | 6 | 11.6 | 9.4-14.5 | 0.28 | .596 | 0.9 |
| No | 80 | 9 | 9.5 | 8.7-10.7 | | | |
| Retroperitoneal metastases | | | | | | | |
| Yes | 20 | 7 | 8.5 | 7.7-10.4 | 1.50 | .221 | 1.1 |
| No | 80 | 9 | 10.5 | 9.4-11.6 | | | |
| Bone metastases | | | | | | | |
| Yes | 26 | 7 | 9.0 | 7.8-11.4 | 2.42 | .120 | 1.2 |
| No | 74 | 9 | 10.3 | 9.2-11.5 | | | |
| Hepatic metastases | | | | | | | |
| Yes | 19 | 5 | 7.4 | 5.5-8.7 | 9.00 | .003 | 1.4 |
| No | 81 | 9 | 10.7 | 9.6-11.8 | | | |
| Total no. of metastatic sites | | | | | | | |
| 0 or 1 | 39 | 10 | 10.7 | 9.2-13.0 | 3.98 | .046 | 1.2 |
| $\geq 2$ | 61 | 8 | 9.4 | 8.4-10.9 | | | |
| Prior therapy | | | | | | | |
| Prior radiation | | | | | | | |
| Yes | 22 | 3 | 8.2 | 7.6-9.5 | 7.59 | .0059 | 1.3 |
| No | 78 | 10 | 10.7 | 9.5-11.9 | | | |
| Prior immunotherapy | | | | | | | |
| Yes | 8 | 4 | 8.2 | 6.2-12.1 | 0.30 | .5863 | 1.1 |
| No | 92 | 9 | 10.3 | 9.2-11.1 | | | |
| Prior chemotherapy | | | | | | | |
| Yes | 10 | 8 | 5.8 | 4.2-8.0 | 13.49 | .0002 | 1.6 |
| No | 90 | 9 | 10.6 | 9.5-11.5 | | | |
| Prior nephrectomy | | | | | | | |
| Yes | 65 | 11 | 11.3 | 9.5-12.7 | 30.40 | .0001 | 1.6 |
| No | 35 | 4 | 8.3 | 6.9-10.0 | | | |
| Interval from initial diagnosis to treatment, years | | | | | | | |
| $< 1$ | 63 | 6 | 8.5 | 7.6-9.4 | 33.74 | .0001 | 1.6 |
| $\geq 1$ | 37 | 13 | 13.8 | 11.8-16.4 | | | |
| $< 2$ | 85 | 6 | 8.8 | 7.9-9.8 | 30.28 | .0001 | 1.7 |
| $\geq 2$ | 25 | 15 | 15.1 | 12.0-18.9 | | | |

The categorical counterparts of the risk factors determined in the model were used to assign each patient to one of three risk groups: those with zero risk factors (favorable-risk), those with one or two (intermediate-risk), and those with three or more (poor-risk). Survival curves for each of these groups were estimated, and the groups were compared using the log-rank test.

### *Validation of Model by Bootstrap Technique*

The predictive performance of the model was internally validated through a two-step nonparametric bootstrapping process.[43] In the bootstrap procedure, the original set of data of size N becomes a parent population from which samples of size N are randomly drawn with replacement. In the first step of internal validation, the bootstrapping technique was used for variable selection. Two hundred bootstrap samples were created, and a stepwise procedure was applied to each sample using the same significance level for entering and removing a variable as in the original model. From this analysis, the percentage of samples for which each variable was included in the model from the 200 samples was calculated. Percent inclusion was used to determine the prognostic importance of a variable because it was expected that a prognostically important variable would be included in the model for a majority of the bootstrap samples. A model was formulated that included all variables whose percent inclusion was greater than or equal to 65%.[44] The models obtained from the stepwise modeling algorithm and the bootstrapping technique were compared.

In the second internal validation step, the bootstrap was used for parameter estimation. Three hundred bootstrap samples were created, and, for each of the samples, the model with the five final variables was refit and the regression parameters and risk ratios were estimated. The sample mean and SD of the 300 risk ratios for each parameter were computed and used to formulate confidence intervals about the risk ratio. These estimates were compared with those quantities obtained in the final Cox model.

**Table 4. Univariate Survival Analysis of Performance Status and Biochemical Parameters**

| | Continuous Form | | Categorical Form | | | |
|---|---|---|---|---|---|---|
| | Parameter Estimate | *P* | Cut Point Used | $\chi^2$ | Risk Ratio | 95% CI |
| Karnofsky performance status | −0.0458 | .0001 | < 80 | 73.62 | 2.15 | 1.80-2.55 |
| Albumin | −0.798 | .0001 | 4 g/dL | 82.05 | 2.12 | 1.80-2.50 |
| Alkaline phosphatase | 0.002 | .0001 | 88/115 U/L* | 25.42 | 1.51 | 1.29-1.78 |
| Hemoglobin | −0.253 | .0001 | 13 g/dL (M)/11.5 g/dL (F) | 88.13 | 2.19 | 1.86-1.78 |
| Lactate dehydrogenase | 0.001 | .0001 | 300 U/L† | 105.14 | 3.32 | 2.64-4.18 |
| Calcium | 0.092 | .1274 | 9 or 11 mg/dL‡ | 28.69 | 1.77 | 1.44-2.18 |
| Corrected calcium | 0.373 | .0001 | 10 mg/dL | 37.59 | 1.98 | 1.59-2.46 |

*Eighty-eight units per liter used for patients ≤ 55 years old at start of treatment and 115 U/L for patients > 55 years old.
†LDH categorized as 1.5 times upper limit of normal.
‡High-risk group defined as < 9 or > 11 mg/dL.

## RESULTS

### *Patient Characteristics and Treatment*

The median age of the patient group was 58 years; 67% were male (Table 2). Sixty-five percent had undergone a prior nephrectomy, 61% had two or more sites of metastases, 22% had received prior radiation therapy, and 18% had received prior immunotherapy or cytotoxic chemotherapy. Thirty-seven percent of patients had an interval from diagnosis to treatment of 1 year or more. Six hundred eight patients (91%) were treated at MSKCC, whereas 62 (9%) were treated at an outside hospital on an MSKCC trial. Treatment consisted of immunotherapy in 396 patients (59%) and chemotherapy (or hormonal therapy) in 274 patients (41%) (Table 1). With regard to immunotherapy, 294 patients were treated with interferon alpha, 68 patients with interleukin-2a, and 34 patients with a combination program. The overall response rate for the 670 patients was 12.5%, which included 10 complete responses and 41 partial responses.

### *Survival Distribution*

The median overall survival time was 10 months (95% confidence interval [CI], 9 to 11 months) (Fig 1). Fifty-seven (8%) of the 670 patients remained alive and the median follow-up time for the survivors was 33 months (range, 0.9 to 187 months). The percentage of patients surviving at 1 year was 42%; the 2- and 3-year survival percentages were 20% and 11%, respectively.

### *Univariate Survival Analysis*

Factors considered in the univariate analyses included number and site of metastases, prior therapy, Karnofsky performance status, and baseline biochemical parameters (Tables 3 and 4). Factors associated with an adverse prognosis included presence of hepatic metastasis, two or more sites of metastases, a Karnofsky performance status less than 80, prior radiation or chemotherapy, lack of prior nephrectomy, and a time interval from disease diagnosis to treatment of less than 1 year. The median survival time according to Karnofsky performance status was 2.7 months for 60%, 6.1 months for 70%, 10.6 months for 80%, and 14.4 months for 90% ($P < .0001$).

The first two columns of Table 4 list parameter estimates and *P* values for testing the association of each biochemical parameter (in its continuous form) with survival. The negative regression coefficients on Karnofsky performance status, serum albumin, and hemoglobin concentrations indicate that, as the values of these three covariates increased, the risk of death decreased. The positive regression coefficients on the other variables indicate that the risk of death increased as the value of the covariate increased. The biochemical parameters found to be significant for an adverse prognosis included low serum albumin, elevated serum alkaline phosphatase, low hemoglobin, an elevated serum lactate dehydrogenase level, and a high corrected serum calcium level. For lactate dehydrogenase, a logarithmic transformation was used to reduce skewness.

The effect on survival of the treatment year and program was evaluated (Table 5). Patients were classified according to treatment with immunotherapy, ie, interferon alpha and/or interleukin-2a, versus chemotherapy (cytotoxics or hormonal therapy) and according to when they received treatment (1975 to 1980, 1981 to 1990, 1991 to 1996). Survival

**Table 5. Effect of Agent and Year of Treatment**

| | No. of Patients | No. of Patients Alive | Median Survival (months) | CI (months) |
|---|---|---|---|---|
| Agent | | | | |
| IFNα/IL-2 | 396 | 48 | 12.9 | 11.5-14.6 |
| Chemotherapy | 274 | 9 | 6.3 | 5.1-7.6 |
| Year of treatment | | | | |
| 1975-1980 | 66 | 1 | 4.2 | 3.3-5.7 |
| 1981-1990 | 370 | 20 | 9.4 | 8.1-10.7 |
| 1991-1996 | 234 | 36 | 13.2 | 11.3-15.2 |

Abbreviations: IFNα, interferon alfa; IL-2, interleukin-2.

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