Interferon-Alfa as a Comparative Treatment for Clinical Trials of New Therapies Against Advanced Renal Cell Carcinoma

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Purpose: **To define outcome data and prognostic criteria for patients with metastatic renal cell carcinoma (RCC) treated with interferon-alfa as initial systemic therapy. The data can be applied to design and interpretation of clinical trials of new agents and treatment programs against this refractory malignancy.**

Patients and Methods: **Four hundred sixty-three patients with advanced RCC administered interferon-α as first-line systemic therapy on six prospective clinical trials were the subjects of this retrospective analysis. Three risk categories for predicting survival were identified on the basis of five pretreatment clinical features by a stratified Cox proportional hazards model.**

Results: **The median overall survival time was 13 months. The median time to progression was 4.7 months. Five variables were used as risk factors for short survival: low Karnofsky performance status, high lactate dehydrogenase, low serum hemoglobin, high corrected serum calcium, and time from initial RCC diagnosis to start of interferon-α therapy of less than one year. Each patient was assigned 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). The median time to death of patients deemed favorable risk was 30 months. Median survival time in the intermediate-risk group was 14 months. In contrast, the poor-risk group had a median survival time of 5 months.**

Conclusion: **Progression-free and overall survival with interferon-α treatment can be compared with new therapies in phase II and III clinical investigations. The prognostic model is suitable for risk stratification of phase III trials using interferon-α as the comparative treatment arm.**

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CLINICAL INVESTIGATION of new agents and combination regimens to identify more effective therapy are of the highest priority for patients with metastatic renal cell carcinoma (RCC).[1-5] For this purpose, interferon-alfa can be considered a suitable treatment for comparison in phase II and phase III RCC clinical trials of promising new agents. Interferon-α has a low but reproducible response proportion and relative tolerability and can be administered in the outpatient setting. A modest survival benefit for this therapy against metastatic RCC has been cited in two recent phase III trials that compared interferon-α to vinblastine or medroxyprogesterone.[6,7] Also, interferon-α is a likely candidate for clinical trials in combination with novel agents, given the highly resistant nature of RCC against chemotherapy.

Determining prognostic factors of survival for patients with advanced RCC is valuable in designing and interpreting results of clinical trials. We have previously reported on a survival and prognostic stratification model derived from 670 patients treated in clinical trials of cytokine or chemotherapy at the Memorial Sloan-Kettering Cancer Center (MSKCC).[8] Systemic treatment for patients in that series was varied, composed of interferon-α, interleukin-2, hormones, and/or chemotherapy, and included patients who had received prior systemic therapy. In that series, we identified a relationship between prior nephrectomy (a risk factor used in the model) and time from initial diagnosis to treatment as prognostic factors for survival.[9] Since that model was derived, two phase III randomized trials have reported a survival benefit for cytoreductive nephrectomy before interferon-α.[10,11] Therefore, the indication for nephrectomy has changed; it is likely that most patients with resectable primary tumors will undergo nephrectomy before cytokine therapy. In the study reported herein, 40% of patients were treated at centers other than MSKCC. We noticed variability in the normal values of the laboratory markers across treatment centers and adjusted our analysis accordingly.

The reduction of heterogeneity caused by various therapies and the assessment of the role of nephrectomy as a risk factor in the light of the randomized trial[10] prompted this analysis. We report on outcome and prognostic factors for survival after interferon-α therapy for 463 previously untreated patients. The outcome data and risk model can be

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Table 1. Summary of Clinical Trial Design, Treatment Program, and Patient Accrual Clinical Trial

Clinical Trial	No. of Patients*	Accrual
Phase II trial of IFN-α 50 MU/m^2 IM 3 d/wk for 12 weeks[12]	26	3/82-4/83
Phase II trial of IFN-α dose escalated from 3 to 9 to 18 MU SC QD until disease progression[12]	40	7/83-4/84
Phase III trial of IFN-α alone versus IFN-α plus vinblastine; IFN-α dose escalated from 3 to 9 to 18 MU SC QD until progression[12]	45	6/84-3/86
Treated with IFN-α alone	22	
Treated with IFN-α plus vinblastine	23	
Phase II trial of IFN-α 5 MU/m^2 SC QD $\times$ 4 d/wk + IL-2 for 2 cycles as induction, then IFN-α 6 MU/m^2 SC 3 d/wk plus IL-2 for 3 weeks as maintenance for 1 to 5 cycles[13]	32	9/89-8/90
Phase II trial of IFN-α dose escalated from 3 to 6 to 9 MU SC QD plus 13-*cis*-retinoic acid until progression[14]	36	1/93-4/94
Phase III trial of IFN-α alone versus IFN-α plus 13-*cis*-retinoic acid; IFN-α dose escalated from 3 to 6 to 9 MU SC QD until progression[15]	284	4/94-7/96
Treated with IFN-α alone	145	
Treated with IFN-α plus CRA	139	

Abbreviations: IFN-α, interferon-α; CRA, 13-*cis*-retinoic acid; IM, intramuscular; SC, subcutaneous; MU, million units; QD, daily.

*Patients were excluded if they had received previous systemic therapy, were registered but ineligible, or were not assessable for survival.

applied to phase II and III clinical trial design, as well as interpretation of novel treatments against RCC.

PATIENTS AND METHODS

Four hundred sixty-three patients with advanced RCC who were treated with interferon-α alone or as part of combination therapy were the subject of this retrospective analysis. All were treated on one of six institutional review board-approved clinical trials at the Memorial Sloan-Kettering Cancer Center (MSKCC) or as part of a multicenter trial coordinated by MSKCC.[12-15] Patients from those studies were included in this analysis if they were assessable for survival and had not received prior systemic therapy, ie, the interferon-α–containing clinical trial represented their first systemic treatment. Accrual for the clinical trials ranged from March 1982 to July 1996. The number of patients derived from each clinical trial, the period of accrual, and a summary of the treatment program are shown in Table 1. Eligibility, treatment programs, and results were reported for the individual trials.[12-15]

Eligibility criteria for all protocols included histologic confirmation of RCC; stage IV disease with measurable lesions; adequate Karnofsky performance status; lack of severe comorbid conditions; and adequate hematologic, renal, and hepatic function. Pretreatment patient characteristics, first date of treatment with interferon-α, best response, date of progression, and date of death or last follow-up were recorded for all patients. Response and progression were defined by standard criteria.[16]

Survival Analysis

Survival time was defined as the time from initiation of treatment to the date of death or last follow-up. Survival distributions were estimated using Kaplan-Meier methodology.[17] Clinical features examined in univariate survival analysis included number and sites of metastases (lung, mediastinum, bone, liver, retroperitoneum), Karnofsky performance status, prior radiation treatment, prior nephrectomy, the time interval from diagnosis to start of treatment, and the selected baseline biochemical features of hemoglobin, serum albumin, alkaline phosphatase, and lactate dehydrogenase (LDH). For each of these four laboratory markers, the normal value of the assay varied across the treatment centers (Table 2). Therefore, for each patient, we used the ratio of the measured value to normal value. The lower limit of normal was used for albumin and hemoglobin and the upper limit was used for LDH and alkaline phosphatase. We also considered corrected calcium concentration in the survival analysis. It was calculated using the formula corrected calcium = total calcium − 0.707[albumin − 3.4] to remove the effects of protein binding and to assess free calcium.

The relationship between survival and each of the variables was analyzed using the log-rank test[18] for categorical variables and a score test based on the Cox proportional hazards model[19] for continuous variables. There were few missing values for any of the variables (none larger than 4%), and in all analyses, case deletion was used to handle

Table 2. Distribution of Laboratory Parameters With Limits of Normal

Baseline Laboratory Parameter	Range of Lower Limit*	Range of Upper Limit*	Values		Ratios	
			Median	Range	Median	Range
Albumin	0.8-4.1 g/dL	2-5.8 g/dL	4	1.8-5.3	1.05	0.51-4.50
Alkaline phosphatase	0-98 U/L	88-450 U/L	104	15-909	0.93	0.14-7.90
Hemoglobin			12.7	6.8-19.7	1.0	0.56-1.66
Male	9-14.8 g/dL	14-18.3 g/dL				
Female	9-14 g/dL	13-18 g/dL				
Lactate dehydrogenase	0-350 U/L	45-955 U/L	178	61-2568	0.81	0.13-11.17

NOTE. Patients were treated at 80 different centers.

*Used lower limit of normal for albumin and hemoglobin and upper limit of normal for alkaline phosphatase and LDH.

the missing values. When necessary, a logarithmic transformation was used to reduce skewness.

Multivariate Model

A significance level of 5% was used as the criterion for the inclusion of a variable in the stepwise modeling procedure. Because this retrospective study included patients in clinical trials from 1982 through 1996, two strata were defined according to when the patient received treatment (1982 to 1990, 1991 to 1996). The stratified Cox proportional hazards model[20] states that the hazard or risk of death at time t for a patient in strata j with variables $x = (x_{1j}, x_{2j}, ..., x_{pj})$ is

$$\lambda_j(t,x) = \lambda_{0j}(t) \exp(\beta_1 x_{1j} + \beta_2 x_{2j} + \ldots + \beta_p x_{pj})$$

where $\lambda_{0j}(t)$ is the baseline hazard function for strata j and β_1, β_2, ..., β_p are the regression coefficients. Using a stepwise modeling algorithm with a .15 significance level for entering and removing explanatory variables, independent risk factors were determined, and the model was formed.

Dichotomization of the continuous variables identified in the model was performed using the minimum P-value approach.[8,21] Using the categorical counterparts of the risk factors, each patient was then assigned 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.[22] 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 modeling. From this analysis, we calculated the percentage of samples for which each variable was included in the model from the 200 samples. 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 contained the five variables with the greatest percent inclusion.[23] 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 SDs of the 300 risk ratios for each parameter were computed and used to formulate confidence intervals (CIs) about the risk ratio. These estimates were compared with those quantities obtained in the final Cox model.

RESULTS

Patient Characteristics and Treatment

The median age was 59 years, and 66% were male (Table 3). Fifty-five percent had undergone prior nephrectomy, and 16% had received prior radiation therapy. Three hundred nineteen (69%) had an interval from initial diagnosis to initiation of treatment with interferon-α of less than 1 year, and 144 (31%) had an interval from initial diagnosis to initiation of treatment of 1 year or greater. Sixty-one percent had two or more sites of metastases. Two hundred seventy-eight (60%) were treated at MSKCC, and 185 (40%) were treated elsewhere on an MSKCC trial. The overall response rate for the 463 patients was 11%, which included 12 complete responses and 41 partial responses.

Baseline Laboratory Parameters

The median of corrected calcium was 9.2, with a range of 6.2 to 12.4. The lower and upper limits of normal values for albumin, alkaline phosphatase, hemoglobin, and LDH varied across 80 centers (Table 2). For example, the lower limit of normal for albumin for one of the centers was 0.8 g/dL, and for another center it was 4.1 g/dL.

Table 3. Patient Characteristics and Best Response

Characteristic	No. of Patients	%
No. of patients	463	
Sex		
Male	307	66
Female	156	34
Age, years		
Median	59	
Range	20-81	
Karnofsky performance status		
60%	2	< 1
70%	92	20
80%	119	26
90%	250	54
Prior therapy		
Nephrectomy	256	55
Radiation	72	16
No. of metastatic sites		
Renal primary or local recurrence only	5	1
1	174	38
2	156	34
3	70	15
≥ 4	58	12
Site of metastatic disease		
Lung	312	67
Mediastinum	120	26
Retroperitoneum lymph nodes	106	23
Bone	108	23
Liver	81	18
Response		
Complete	12	3
Partial	41	9
Stable	227	49
Disease progression	149	32
Not assessable for response	34	7

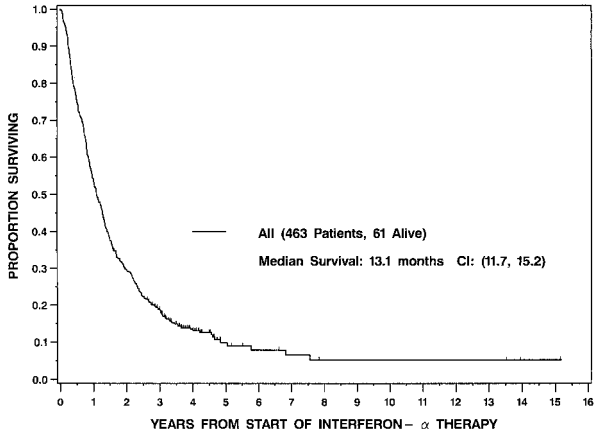

Fig 1. Survival time in 463 patients with advanced RCC treated with interferon-α; 61 patients were alive at last follow-up, indicated by |.

Overall and Progression-Free Survival Distribution

The median overall survival time was 13 months (95% CI, 12 to 15 months) (Fig 1). Sixty-one (13%) of the 463 patients remain alive, and the median follow-up time for survivors was 46 months (range, 1 to 181 months). The proportion of patients surviving at 1 year was 54%. The 2-year, 3-year, and 5-year survival proportions were 30%, 19%, and 10%, respectively.

Fifty-seven patients remained progression-free after treatment with interferon-α at last follow-up. The median progression-free survival time was 4.7 months (95% CI, 4.1 to 5.3 months) (Fig 2). The proportions of progression-free patients at 4, 6, 12, 24, and 36 months were 55%, 42%, 24%, 14%, and 8%, respectively.

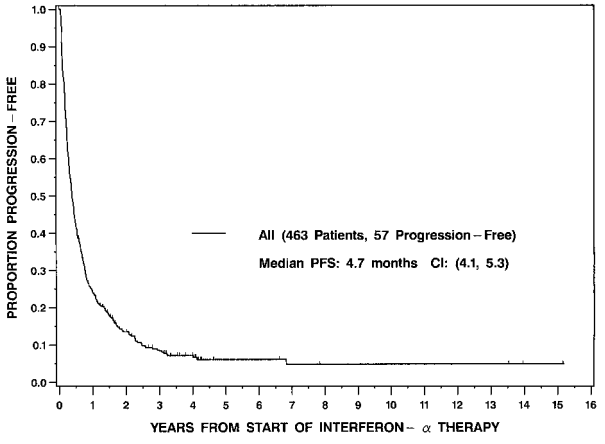

Fig 2. Progression-free survival in 463 patients with advanced RCC treated with interferon-α; 57 remain progression-free at end of follow-up, indicated by |.

Univariate Survival Analysis

Factors considered in the univariate survival analyses included number and site of metastases, prior nephrectomy, prior radiotherapy, Karnofsky performance status, and baseline biochemical parameters (Tables 4 and 5). Clinical features associated with an adverse prognosis included presence of hepatic metastasis, Karnofsky performance status less than 80%, lack of prior nephrectomy, and a time interval from disease diagnosis to treatment of less than 1 year.

The biochemical parameters found to be significant for an adverse prognosis included low serum albumin, elevated serum alkaline phosphatase, low hemoglobin, elevated serum LDH level, and a high corrected serum calcium level.

Multivariate Survival Analysis

The nine variables outlined above were included in the multivariate analysis. The five most significant risk factors that predicted survival were hemoglobin, LDH, corrected calcium, Karnofsky performance status, and interval from diagnosis to treatment. Liver metastases reached a marginal significance level ($P = .02$) and was not kept in the final model.

Risk Groups

Five risk factors were used to create the risk model: low Karnofsky performance status ($< 80\%$), high LDH (> 1.5 times the upper limit of normal), low serum hemoglobin, high corrected serum calcium (> 10 mg/dL), and time from initial diagnosis to interferon-α of less than 1 year. The cut-points for LDH and hemoglobin were found by the minimum *P*-value approach.[8,21] A Cox model was fit using the categorical versions of the variables (Tables 6 and 7). Each patient was then assigned 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).

There was a significant difference in the survival profiles of the three risk groups ($P < .0001$) (Fig 3). The median survival time for the 18% of favorable-risk patients was 30 months, and the 1-year, 2-year, and 3-year survival rates were 83%, 55%, and 45%, respectively. Sixty-two percent of patients were in the intermediate-risk group, and the median survival time for this group was 14 months, with 1-year, 2-year, and 3-year survival rates of 58%, 31%, and 17%, respectively. The poor-risk group comprised 20% of patients and had a median survival of 5 months, with 1-year, 2-year, and 3-year survival rates of 20%, 6%, and 2%.

Progression-free survival for patients was calculated according to risk group. The median progression-free survival increased from 2.5 to 5.1 to 8.3 months in poor-risk, intermediate-risk, and favorable-risk groups, respectively (Table 8).

Table 4. Univariate Survival Analysis of Number and Sites of Metastases and Prior Therapy

	%	Censored (%)	Survival (months)		χ^2	*P*	Risk Ratio
			Median	CI			
Prior nephrectomy							
Yes	55	17	16.8	14.4-19.1	25.27	.0001	1.7
No	45	8	10.6	9.2-12.2			
Prior radiation							
Yes	16	11	13.1	9.7-17.3	0.003	.9561	1.0
No	84	14	13.3	11.4-15.5			
Bone metastases							
Yes	23	11	13.1	10.7-16.0	0.18	.6713	1.1
No	77	14	13.1	11.3-15.5			
Lung metastases							
Yes	67	14	13.1	11.5-15.6	0.89	.3459	0.9
No	33	11	13.1	9.7-15.8			
Liver metastases							
Yes	17	10	8.1	5.2-10.2	10.72	.0011	1.5
No	83	14	14.8	13.0-16.1			
Mediastinal metastases							
Yes	26	12	15.3	12.2-17.5	0.02	.9006	1.0
No	74	14	12.4	11.1-14.7			
Retroperitoneal metastases							
Yes	23	10	9.5	7.8-12.4	3.6	.0577	1.3
No	77	14	14.8	13.0-16.2			
No. of metastatic sites							
≤ 1	39	13	14.6	12.0-16.2	0.59	.4415	1.1
> 1	61	13	12.6	11.0-15.2			
Interval from initial diagnosis to treatment							
< 1 year	69	9	10.7	9.5-12.2	28.62	.0001	1.8
≥ 1 year	31	22	19.3	16.4-24.9			
< 2 years	78	11	11.4	10.1-13.1	17.48	.0001	1.7
≥ 2 years	22	22	20.2	17.8-28.0			

Bootstrap Validation

For the first step of validation, the five variables with the greatest percent inclusion were hemoglobin, LDH, corrected calcium, Karnofsky performance status, and time from diagnosis to treatment (Table 9). The results of this model selection technique confirmed the variables chosen in the original modeling procedure. Of note, percent inclusion for the variable interval from diagnosis to treatment was 85%, compared with 29% for prior nephrectomy.

In the second step of validation for each covariate in the final model, a risk ratio with a 95% CI was estimated. Risk ratios were similar to those obtained in the original multi-

Table 5. Univariate Survival Analysis of Performance Status and Biochemical Parameters

	Continuous Form		Categorical Form		
	Parameter Estimate	*P*	Cutpoint Used	χ^2	Risk Ratio
Karnofsky performance status	−0.0265	.0001	80	21.83	1.73
Ratio albumin*	−3.4795	.0001	Lower limit of normal	26.59	1.74
Ratio alkaline phosphatase*	0.7794	.0001	Upper limit of normal	21.33	1.61
Ratio hemoglobin*	−5.5323	.0001	Lower limit of normal	29.68	1.74
Ratio lactate dehydrogenase*	1.4796	.0001	1.5 × upper limit of normal	56.82	3.50
Calcium	0.1015	.2015	9 or 11 mg/dL†	6.35	1.40
Corrected calcium	0.3640	.0001	10 mg/dL	29.03	2.18

*Logarithmic forms of the ratios used.

†High-risk group defined as < 9 or > 11.

Table 6. Results of Multivariate Analysis

	Parameter Estimate	SE	χ^2	P	Risk Ratio	95% CI
Lactate dehydrogenase	1.1715	0.1734	45.65	.0001	3.23	2.30-4.53
Hemoglobin	0.4232	0.1053	16.14	.0001	1.53	1.24-1.88
Corrected calcium	0.6561	0.1459	20.23	.0001	1.93	1.45-2.57
Karnofsky performance status	0.4153	0.1283	10.48	.0012	1.52	1.18-1.95
Interval from initial RCC diagnosis to IFN-α treatment*	0.3914	0.1184	10.93	.0009	1.48	1.17-1.87

*Less than 1 year versus $\geq$ 1 year.

variate model (data not shown). The results of these two steps provide evidence of the robustness of the model-building process.

DISCUSSION

Interferon-α and interleukin-2 show a low degree of antitumor effect against RCC.[1,5] Outcome data from either cytokine may be considered in clinical trial design and interpretation of new therapies. Patients treated with high-dose bolus interleukin-2 have been reported to achieve durable responses.[24] However, treatment-related toxicity can be severe, mandating stringent patient selection, intensive supportive care, and specialized treatment centers; therefore, its use as the comparative treatment arm in phase III trials limits both center and patient participation. Also, the patient population selected to tolerate the intensive therapy may differ from those deemed appropriate for the investigational therapy. In contrast, interferon-α is administered as outpatient therapy and can be used in a less restricted patient population. Several recently reported phase III trials in advanced RCC used interferon-α as the compared treatment arm.[15,25-29]

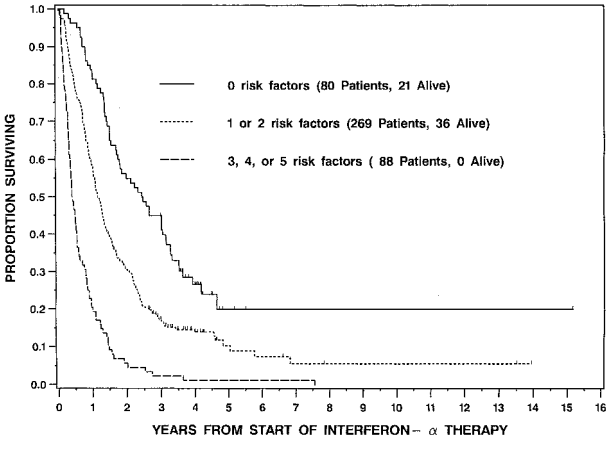

Fig 3. Survival stratified according to risk group (N = 437); 26 patients who were missing one or more of the five risk factors were excluded. | indicates last follow-up.

The determination of prognostic factors for survival in patients with advanced RCC is vital in designing and interpreting phase III randomized clinical trials. In this report, survival data and a model for assessing outcome and prognosis for patients treated with interferon-α as first-line systemic therapy is provided. We have previously reported on a survival and prognostic stratification model derived from 670 patients treated in clinical trials of cytokine or chemotherapy at our center.[8] The prognostic model based on first-line interferon-α therapy included the same risk factors as the previously published model did,[8] except the no-prior-nephrectomy risk factor was replaced with time from initial diagnosis to interferon-α treatment of less than 1 year.

The role of cytoreductive nephrectomy for patients with stage IV RCC has been controversial.[5] The longer survival time in patients after nephrectomy[12] was predominantly linked with a long disease-free interval in patients who underwent surgical resection for a localized tumor and subsequently relapsed, which reflected a more indolent tumor biology when compared with survival of patients who presented de novo with a renal primary tumor and clinical evidence of metastases.[9] Two recent randomized trials showed an improvement in survival for patients who undergo nephrectomy versus no surgery before treatment with interferon-α.[10,11] The improvement in survival was greatest for patients with high performance status and metastases confined to lung.[10]

On the basis of the results of these trials,[10,11] selected patients with stage IV RCC will undergo nephrectomy before cytokine therapy. The indication for nephrectomy has changed in standard management from that used in the previously reported model,[8] and it is likely that many more patients will undergo nephrectomy before interferon-α (or other cytokine) therapy. Therefore, the substitution of time from initial RCC diagnosis to interferon-α therapy for nephrectomy as a risk factor in our model is indicated.

Investigational therapies with immunotherapy, angiogenesis inhibition, or other novel treatment strategies could show an antitumor effect by producing prolonged stabilization of disease or slow tumor regression during many

Table 7. Results According to Risk Factors

No. of Risk Factors	%*	Alive (%)	Survival (months)		1-Year Survival (%)	3-Year Survival (%)
			Median	95% CI		
0	18	26	29.6	20.9, 37.8	83	45
1 or 2	62	13	13.8	12.4, 15.9	58	17
3, 4, or 5	20	0	4.9	4.3, 6.3	20	2

*N = 437; 26 patients are missing one or more of the five risk factors.

Table 8. Progression-Free Survival According to Risk Model

No. of Risk Factors	%*	Progression Free (%)	PFS (months)		6-Month PFS (%)	12-Month PFS (%)
			Median	95% CI		
0	18	10	8.3	6.0-12.0	60	39
1 or 2	62	14	5.1	4.3-6.2	45	24
3, 4, or 5	20	10	2.5	1.5-2.8	19	10

Abbreviation: PFS, progression-free survival.
*N = 437; 26 patients are missing one or more of the five risk factors.

Table 9. Percent Inclusion of Each Variable in Variable Selection Step of Bootstrap Validation

HGB*	LDH*	Corrected Calcium	Time From Diagnosis to Treatment	KPS	Hepatic Mets	Nephrectomy	Alkaline Phosphatase*	Albumin*
100	100	98.5	84.5	84.5	82	28.5	24.5	22

Abbreviations: KPS, Karnofsky performance status; HGB, hemoglobin.
*Logarithmic form of the ratio used.

months.[30] Therefore, phase II and III clinical trials of these agents against RCC may investigate progression-free survival as an end point of treatment outcome. The 4-month and 6-month progression-free survival rates associated with interferon-α therapy were 55% and 42%, respectively. These rates can be used for designing future clinical trials of novel agents including angiogenesis inhibitors. Reporting of prognostic factors in phase II trials should be encouraged, as these factors help interpret outcome for a given patient population.

The outcome data from interferon-α and the risk model derived from this study can be applied to the design and interpretation of phase II and III trials of new agents or combination programs against metastatic RCC. Several aspects of this analysis warrant comment and continued study. First, validation of the risk model was performed by the bootstrap method.[22] Repeated sampling of the original data with replacement allowed independent samples of RCC patients to be generated from which the robustness of the model-building process was assessed. Validation of the model on an external data set would be useful.

Second, several prognostic models obtained by multivariate analyses in patients with metastatic RCC have been reported.[31-36] These have been reviewed and compared with the MSKCC model.[8] In this regard, a consensus on prognostic criteria for metastatic RCC is warranted. Third, recent progress in understanding of genetic features of RCC has facilitated classification into clear-cell and non–clear-cell subtypes (papillary, chromophobe, collecting duct).[1] Specification of RCC histology into subtypes was not a part of this analysis. However, review of pathology of 109 patients treated at MSKCC with interferon-α on the most recent trial[15] included in this analysis identified eight patients (7%) with non–clear-cell histology (six chromophobe, two collecting duct). The relative sensitivity of RCC cell subtypes to interferon-α remains to be determined.

In summary, the low proportion of patients with advanced RCC achieving long-term survival emphasizes the need for clinical investigation to identify more effective therapy. Progression-free and overall survival for interferon-α treatment can be used as a baseline for assessment of new therapies in phase II and III clinical investigations. The prognostic model is suitable for risk stratification of phase III trials using interferon-α as the comparative treatment arm and single-arm phase II trials to study progression-free survival as an end point.

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