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ORIGINAL REPORT

Validation and Extension of the Memorial Sloan-Kettering Prognostic Factors Model for Survival in Patients With Previously Untreated Metastatic Renal Cell Carcinoma

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ABSTRACT

Purpose
To validate the Motzer et al prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma (RCC) and to identify additional independent prognostic factors.

Patients and Methods
Data were collected on 353 previously untreated metastatic RCC patients enrolled onto clinical trials between 1987 and 2002.

Results
Four of the five prognostic factors identified by Motzer were independent predictors of survival. In addition, prior radiotherapy and presence of hepatic, lung, and retroperitoneal nodal metastases were found to be independent prognostic factors. Using the number of metastatic sites as surrogate for individual sites (none or one *v* two or three sites), Motzer's definitions of risk groups were expanded to accommodate these two additional prognostic factors. Using this expanded criteria, favorable risk is defined as zero or one poor prognostic factor, intermediate risk is two poor prognostic factors, and poor risk is more than two poor prognostic factors. According to Motzer's definitions, 19% of patients were favorable risk, 70% were intermediate risk, and 11% were poor risk; median overall survival times for these groups were 28.6, 14.6, and 4.5 months, respectively ($P < .0001$). Using the expanded criteria, 37% of patients were favorable risk, 35% were intermediate risk, and 28% were poor risk; median overall survival times of these groups were 26.0, 14.4, and 7.3 months, respectively ($P < .0001$).

Conclusion
These data validate the model described by Motzer et al. Additional independent prognostic factors identified were prior radiotherapy and sites of metastasis. Incorporation of these additional prognostic factors into the Motzer et al model can help better define favorable risk, intermediate risk, and poor risk patients.

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INTRODUCTION

In the United States, renal cell carcinoma (RCC) accounts for 2.5% of the cancer incidence and 2% of the cancer mortality.[1] Recent epidemiologic studies suggest that the incidence of all stages of RCC is increasing.[2] Approximately 30,000 new cases of RCC are diagnosed in the United States each year.[3] RCC can be cured surgically if detected at an early stage. The estimated 5-year survival for patients with disease confined to the kidney (stages T1 and T2) is approximately 90% to 95%.[4,5] However, once metastatic disease

Table 1. Motzer et al[13] Model

Factors Included	Poor Prognostic Group
KPS	< 80
Time from diagnosis to treatment with interferon alfa, months	< 12
Hemoglobin	< Lower limit of laboratory's reference range
Lactate dehydrogenase	> 1.5× upper limit of laboratory's reference range
Corrected serum calcium, mg/dL	> 10.0

NOTE. Risk groups are defined as follows: favorable, no poor prognostic factors present; intermediate, one or two poor prognostic factors present; poor, more than two poor prognostic factors present.
Abbreviation: KPS, Karnofsky performance status.

develops, the prognosis for long-term survival is poor, with 5-year survival ranging between 0% and 20%.[3,4,6]

Unfortunately, approximately one third of patients have metastatic disease at the time of diagnosis, and approximately 50% of patients undergoing potentially curative surgery for less advanced disease can be expected to relapse distantly.[4,5] Coupled with the lack of effective systemic therapy and the highly variable natural history of RCC, the poor outlook for patients with metastatic disease highlights the need to better define patient and disease factors that are associated with outcome. Identification of a reliable, validated prognostic model for outcome in patients with metastatic RCC will yield an important tool that can be used to help optimize patient selection for specific treatment strategies and aid in the interpretation of clinical trials by helping to determine the extent to which therapy is impacting the natural history of the disease.

Reports in the literature vary with respect to the identification of patient and disease characteristics that are prognostic for survival in patients with metastatic RCC.[7-15] Although some factors have consistently been found to be of prognostic value (eg, performance status [PS]), all of the reports have evaluated different sets of factors, and definitions of some factors, such as metastasis-free interval, have varied.

Recently, Motzer et al[13] identified five prognostic factors that correlated with overall survival in patients with metastatic RCC treated with interferon alfa as initial systemic therapy. The factors were Karnofsky PS, time from diagnosis of RCC to treatment with interferon alfa, serum lactate dehydrogenase, corrected serum calcium, and hemoglobin. Using a dichotomized version of each factor and giving them all equal weight, Motzer et al stratified patients into three different risk groups (favorable, intermediate, and poor risk) depending on the number of poor prognostic factors present (Table 1). The model was validated internally using a bootstrap resampling procedure; however, external validation in an independent set of patients would provide a valuable confirmation of the model before it is adopted and used in the design of future clinical trials in this disease.

The primary goal of this investigation was to validate the model developed by Motzer et al[13] in an independent group of patients using survival as the primary end point. However, given the varied reports of prognostic factors for survival in the literature, we also considered all previously reported factors that are readily available as part of the patient's normal work-up to determine whether additional independent prognostic factors could be identified that could be used to extend or modify the model.

PATIENTS AND METHODS

Records of metastatic RCC patients previously untreated with systemic therapy, who were enrolled onto institutional review board–approved clinical trials at the Cleveland Clinic Foundation between April 1987 and April 2002, were reviewed. The trials were primarily phase I and II studies of investigational agents or combination therapies. Eligibility criteria for the trials were fairly uniform and generally included the following: histologic documentation of RCC; clinical or biopsy evidence of metastatic disease; bidimensionally measurable disease; Eastern Cooperative Oncology Group (ECOG) PS of less than or equal to 1; normal renal, hepatic, and bone marrow; absent or stable CNS metastasis; no prior history of cancer (except basal cell carcinoma or carcinoma-in-situ of the cervix); absence of significant cardiac disease; and no recent surgery. Data collected included standard pretreatment patient and disease characteristics, baseline biochemical parameters, first date of treatment, best response to treatment, date of progression, date of death or last follow-up, and other factors previously reported as being prognostic for survival in patients with metastatic RCC (Table 2). Response and progression were defined by standard criteria.[16] Survival was defined as the time from initiation of treatment to the date of death or last follow-up.

Survival distributions were estimated using the Kaplan-Meier method.[17] The relationship between survival and the factors listed in Table 2 were analyzed using the log-rank test[18] and the Cox proportional hazards model.[19] Clinical and pathologic characteristics that were categoric by nature, such as sex, PS, and histology, were individually analyzed using the log-rank test. Biochemical parameters and other characteristics that are measured on a continuum, such as age and time from diagnosis to study entry, were individually analyzed as continuous variables using the Cox proportional hazards model and as categoric variables using the log-rank test. The cut points used for categorizations were based on cutoffs previously described in the literature and/or recursive partitioning. The Cox proportional hazards model with stepwise variable selection was used to simultaneously assess multiple factors. A significance level of $P = .10$ was used as the criterion for determining variable entry and removal from the model. Because patients were treated over a fairly long period of time, the stratified version of the model was used to adjust for any inherent changes in prognosis over time. The treatment periods used to define the strata were 1987 to 1991, 1992 to 1996, and 1997

Table 2. Potential Prognostic Factors Considered

Demographic and Clinical Factors	Biochemical and Hematologic	Histologic
Sex	Serum albumin (g/dL)	Histology
Age at diagnosis	Serum alkaline phosphatase (U/L)	Nuclear grade
Age at study entry	Serum lactate dehydrogenase (U/L)	
ECOG PS	Serum calcium (mg/dL)	
Time from diagnosis to study entry	Corrected serum calcium (mg/dL)	
Prior nephrectomy	Serum creatinie (mg/dL)	
Prior radiotherapy	Hemoglobin (g/dL)	
Kidney initially involved	Neutrophil count (K/μL)	
Lung metastasis		
Mediastinal metastasis		
Hepatic metastasis		
Osseous metastasis		
CNS metastasis		
Retroperitoneal lymph node metastasis		
Other metastatic sites		
Number of metastatic sites		
Year of entry onto study		

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

to 2002. For convenience, only the categoric forms of continuous variables were included in the multivariable analyses.

RESULTS

Three hundred fifty-three patients with no prior history of treatment with systemic therapy who were enrolled onto institutional review board–approved clinical trials between April 1987 and April 2002 were identified. Excluding patients with incomplete information on the five prognostic factors included in the Motzer et al[13] model, a total of 308 patients were available for analysis. Table 3 lists the therapies patients were treated with on different clinical trials.[20-36] Patients received a variety of single agents and combination therapies; however, the majority of patients (77%) was treated with immunotherapy alone, primarily with interleukin-2– or interferon alfa–based regimens (56%). Twenty-three percent of patients received chemotherapy with or without immunotherapy, which primarily involved combination fluorouracil, interleukin-2, and interferon alfa or capecitabine plus interferon alfa.

Tables 4 and 5 list the patient and disease characteristics and the biochemical factors examined. Seventy-three percent of the patients were male, and median age at diagnosis was 54 years (range, 23 to 76 years). Most patients (81%) had prior nephrectomy and most were entered onto a clinical trial within a few months of their initial diagnosis (median, 4.2 months). By design, patients tended to have good PS (all were ambulatory with ECOG PS of 0 or 1), and few patients (4%) had CNS metastases.

Although an attempt was made to capture the histology and nuclear grade of the primary tumor, complete information was often not available. Of the 267 patients (87%) with histology available, 85% had clear-cell tumors, and 15% had other histologies, primarily papillary and sarcomatoid features. One hundred seventy-one patients had information on nuclear grade; 28% of these tumors were grade 1 or 2, and 72% were grade 3 or 4.

Median survival time for the 308 patients studied was 14.8 months. Eighty-one percent of the patients had died by the time of analysis, and 19% were still alive or had been lost

Table 3. Study Treatments

Therapy	No. of Patients	Reference
Immunotherapy		
IL-2 and/or interferon based		
IL-2 + TIL	20	Figlin et al[20]
IL-2 + IFN-α	55	Bukowski et al[21]
IL-2 + IFN-α + GM-CSF	49	Agrawal et al[22]
SC IL-2	8	—*
IL-2 + Peg IFN-α	23	Hutson et al[23]
IL-2 + thalidomide	3	Olencki et al[24]
IFN-α + IL-12	8	Motzer et al[25]
Consensus IFN-α	5	Hutson et al[26]
IFN-β	1	Bukowski et al[27]
Total		
No.	172	
%	56	
Other immunotherapy		
Adoptive immunotherapy	20	Plautz et al[28]
IL-12	18	Motzer et al[29]
TIL	13	—*
IL-6 + GM-CSF	5	Tate et al[30]
GM-CSF	5	Wos et al[31]
Leuvectin	1	Thompson et al[32]
PCL	2	—*
Total		
No.	64	
%	21	
Chemotherapy +/− immunotherapy		
FU + IFN-α + IL-2	33	Olencki et al[33]
Capecitabine + IFN-α	23	Chang et al[34]
Gemcitabine + IFN-α	6	Perez-Zincer et al[35]
FUDR ± IFN-α	8	—*
Taxoprexin	2	Schacter et al[36]
Total		
No.	72	
%	23	

Abbreviations: IL, interleukin; TIL, tumor-infiltrating lymphocytes; IFN-α, interferon alfa; GM-CSF, granulocyte-macrophage colony-stimulating factor; Peg, pegylated; PCL, hydrastatic pressure combined with membrane protein cross-linking modified tumor cells; FU, fluorouracil; FUDR, floxuridine; SC, subcutaneous.
*Not published.

Table 4. Patients Characteristics: Categorical

Factor	Patients		Deaths (%)	1-Year Survival (%)		Median Survival (months)	*P**
	No.	%		Mean	SD		
Overall	308	100	81	57	3	14.8	—
Sex							
Male	224	73	79	57	3	14.8	—
Female	84	27	85	57	5	14.6	.59
ECOG PS							
0	125	41	71	68	4	20.7	—
1	183	59	87	50	4	12.2	.002
Prior nephrectomy							
No	58	19	93	34	6	8.4	—
Yes	250	81	78	63	3	16.4	< .001
Prior radiotherapy							
No	255	83	80	60	3	15.8	—
Yes	53	17	83	47	7	11.4	.03
Involved kidney							
Right	148	48	77	61	4	15.5	—
Left	155	50	83	53	4	13.1	.17†
Bilateral	5	2	80	100		20.1	—
Lung metastasis							
No	81	26	81	64	5	16.1	—
Yes	227	74	80	55	3	14.1	.77
Mediastinal metastasis							
No	217	71	79	57	3	15.4	—
Yes	91	29	85	58	5	13.9	.75
Hepatic metastasis							
No	244	79	77	63	3	16.6	—
Yes	64	21	94	35	6	7.5	< .001
Osseous metastasis							
No	214	69	79	60	3	16.2	—
Yes	94	31	85	53	5	12.7	.11
CNS metastasis							
No	297	96	81	58	3	14.8	—
Yes	11	4	82	45	15	8.4	.97
Retroperitoneal lymph node metastasis							
No	227	74	80	63	3	16.6	—
Yes	81	26	81	41	6	9.8	.03
Other metastatic sites‡							
No	222	72	83	57	3	14.5	—
Yes	86	28	74	58	5	15.4	.79
Histology							
Clear cell	227	74	78	65	3	17.0	—
Other§	40	13	88	26	7	8.0	< .001‖
Unknown	41	13	88	47	8	11.0	—
Nuclear grade							
1/2	48	16	62	68	7	15.8	.004¶
3/4	123	40	83	48	5	11.4	—
Unknown	137	44	85	62	4	16.6	—
Year of trial entry							
1987-1991	59	19	95	48	7	11.1	—
1992-1996	96	31	94	53	5	13.6	—
1997-2002	153	50	67	64	4	17.0	.40#

Abbreviations: SD, standard deviation; ECOG PS, Eastern Cooperative Oncology Group performance status.
*Log-rank test.
†Comparison of right- versus left-sided tumors.
‡The most commonly reported other sites were adrenal(s), opposite kidney, pancreas, supraclavicular nodes, and spleen.
§Primarily papillary.
‖Comparison of clear cell versus other histologies.
¶Comparison of grade 1 to 2 versus 3 to 4.
#Test for trend, $P = .21$.

Table 5. Patient Characteristics: Continuous*

Factor	Patients No.	Patients %	Deaths (%)	1-Year Survival (%) Mean	1-Year Survival (%) SD	Median Survival (months)	P†
Age at diagnosis, years							
Mean	54.0		80				
SD	10.7						
Median	54		72				.73
Range	23-76						
≤ 60 years	212	69	80	59	3	14.7	
> 60 years	96	31	72	54	5	15.4	.29
Age at trial entry, years							
Mean	56.2						
SD	10.5						
Median	56						.24
Range	24-77						
≤ 60 years	189	61	82	56	4	14.4	
> 60 years	119	39	78	60	5	16.4	.41
Diagnosis to trial entry, months							
Mean	26.5						
SD	49.2						
Median	4.2						.001
Range	0-278.9						
< 12 months	196	64	83	49	4	11.4	
≥ 12 months	112	36	76	72	4	21.8	< .001
No. of metastatic sites							
Median	2						< .001
Range	1-6						
1 or 2	215	70	79	63	3	17.1	
> 2	93	30	85	44	5	9.8	.005
Albumin, g/dL‡							
Mean	4.1						
SD	0.6						
Median	4.1						< .001
Range	2.5-8.9						
< LLN	38	12	92	23	7	6.2	
≥ LLN	270	88	79	62	3	17.1	< .001
Alkaline phosphatase, g/dL§							
Mean	122.5						
SD	105.0						
Median	97						.10
Range	32-1,333						
≤ ULN	218	71	78	67	3	18.3	
> ULN	90	29	86	35	5	8.1	< .001
Lactate dehydrogenase, U/L‖							
Mean	206.8						
SD	138.6						
Median	171						< .001
Range	12-1,338						
≤ 1.5 × ULN	282	92	80	61	3	15.8	
> 1.5 × ULN	26	8	88	19	8	3.4	< .001
Calcium, mg/dL¶							
Mean	9.5						
SD	0.9						
Median	9.4						.08
Range	3.5-13.1						
< LLN or > ULN	33	11	94	28	8	8.7	
Within normal limits	275	89	79	61	3	16.1	< .001
Corrected calcium, mg/dL#							
Mean	9.0						
SD	1.0						
Median	8.9						< .001
Range	0.3-13.4						
≤ 10 mg/dL	280	91	80	61	3	15.8	
> 10 mg/dL	28	9	91	20	8	5.4	< .001

(continued on following page)

Table 5. Patient Characteristics: Continuous* (continued)

Factor	Patients No.	Patients %	Deaths (%)	1-Year Survival (%) Mean	1-Year Survival (%) SD	Median Survival (months)	*P*†
Creatinine, mg/dL							
Mean	1.2						
SD	0.3						
Median	1.2						.86
Range	0.6-3.7						
≤ 1.5 mg/dL	258	84	81	58	3	14.7	
> 1.5 mg/dL	50	16	76	54	7	17.0	.53
Hemoglobin, g/dL**							
Males							
Mean	12.6						
SD	2.0						
Median	12.8						< .001
Range	6.7-18.6						
< LLN	149	66	85	50	4	11.4	
≥ LLN	75	33	68	73	5	25.5	< .001
Females							
Mean	12.0						
SD	2.0						
Median	12.1						< .001
Range	4.3-17.2						
< LLN	41	49	92	41	8	9.0	
≥ LLN	43	51	79	74	7	21.9	< .001
Total							
Mean	12.4						
SD	2.0						
Median	12.6						
Range	4.3-18.6						< .001††
< LLN	190	62	86	48	4	11.1	
≥ LLN	118	38	72	73	4	24.7	< .001
Neutrophil count, K/μL‡‡							
Mean	5.4						
SD	2.7						
Median	4.9						
Range	1.3-27.8						< .001§§
≤ ULN	254	83	80	61	3	15.8	
> ULN	34	11	76	36	9	5.2	.15§§
Unknown	20	6	90	49	11	11.4	

Abbreviations: SD, standard deviation; LLN, lower limit of laboratory's reference range; ULN, upper limit of laboratory's reference range; CCF, Cleveland Clinic Foundation.
*Almost all patients' baseline laboratory tests were performed at CCF, and therefore only CCF reference ranges are reported here.
†Log-rank test for categorical form of the variable and Cox proportional hazards model for continuous form of the variable.
‡Albumin: lower limit of reference range was 3.5 g/dL.
§Alkaline phosphatase: upper limit of reference range was 120 U/L.
‖Lactate dehydrogenase: upper limit of reference range was 220 U/L.
¶Calcium: reference range was 8.5 to 10.5 mg/dL.
#Corrected calcium = total calcium − 0.707 (albumin − 3.4).
**Hemoglobin: lower limits of reference range for men and women were 13.5 and 12.0 g/dL, respectively.
††Stratified by sex.
‡‡Neutrophil count: upper limit of reference range was 7.7 K/μL.
§§Ignores patients with unknown neutrophil counts.

to follow-up. Median follow-up time for these 60 patients was 17.9 months (range, 1 month to 14.1 years).

To validate the model proposed by Motzer et al[13] and to determine whether additional factors could be identified to either extend or otherwise modify this model, a stepwise stratified Cox proportional hazards model, which considered the categoric forms of the factors listed in Tables 4 and 5, was used. However, histology and nuclear grade were not considered at this stage because of the large proportion of patients missing this information. Prior nephrectomy and total serum calcium were also not considered because prior nephrectomy is highly correlated with time from diagnosis to entry onto study (only one of the 58 patients who had prior nephrectomy was diagnosed with RCC more than 12

months before entering a clinical trial), and corrected calcium[37] is highly correlated with total calcium (Pearson's correlation coefficient, $r = 0.92$). The results of this analysis are listed in Tables 6 and 7. Using a significance level of $P = .10$ for determining variable entry into and deletion from the model, four of the five factors identified by Motzer et al were again identified as being independent prognostic factors for survival, time from diagnosis to entry onto study, hemoglobin, corrected serum calcium, and serum lactate dehydrogenase. PS, which was an important predictor in the Motzer et al model, was not found to be a statistically significant predictor. This was not surprising, however, because all patients in the current series had an ECOG PS of 0 or 1, and therefore, all patients had a favorable PS based on Motzer et al's categorization.

Using the risk groups as defined by Motzer et al,[13] 58 patients (19%) had no poor prognostic factors present and, therefore, were categorized as favorable risk; 70% of patients had one or two poor prognostic factors present and, therefore, were considered intermediate risk; and 11% of patients were categorized as poor risk because more than two poor prognostic factors were present. Median survival times were 28.6, 14.6, and 4.5 months for the favorable, intermediate, and poor risk groups, respectively ($P < .0001$). These figures are similar to those reported by Motzer et al; 18% of 437 patients analyzed were favorable risk and had a median survival of 29.6 months, 62% of patients belonged to the intermediate risk group, which had a median survival of 13.8 months, and 20% of patients were considered poor risk and had a median survival of 4.9 months. Survival curves for the three risk groups as defined by Motzer et al are given in Figure 1.

In addition to the prognostic factors identified by Motzer et al,[13] prior radiotherapy ($P < .001$) and the presence of hepatic metastases ($P < .001$), metastases to the lung ($P = .003$), and retroperitoneal nodal metastases ($P = .04$) were also observed to have a negative impact on survival. As a surrogate for the individual metastatic sites, the number of sites was also considered. Replacing the individual metastatic sites with the number of sites involved (zero or one *v* two or three sites) did not result in any appreciable loss of information based on the log partial likelihood, and therefore, in the final model, the number of metastatic sites was used rather than the individual sites. In addition to being an excellent surrogate for the individual sites of metastatic disease, the number of sites involved also provides an easy way to extend the Motzer et al model. That is, by again simply counting the number of poor prognostic factors present, three new risk groups can be defined. The favorable risk group now contains patients with zero or one poor prognostic factor, the intermediate group contains patients with two poor prognostic factors present, and the poor risk group contains patients with three or more poor prognostic factors present.

The result of applying the extended model and the new definitions of risk groups is summarized in Tables 7 and 8. On the basis of the extended model and the new risk group definitions, the favorable risk group is comprised of 37% of the 308 patients and has an estimated median survival of 26.0 months. Thirty-five percent of patients now fall into the intermediate risk group, which has a median survival of 14.4 months, and 28% of patients are considered poor risk and have a median survival of 7.3 months ($P < .001$).

As can be seen from Tables 7 and 8, the new stratification essentially identifies and reclassifies as favorable and poor risk the better and poorer prognosis patients originally considered to be intermediate risk. For example, from Table 8, 58 patients who were considered to be intermediate risk as originally defined by Motzer et al[13] were considered favorable risk by the new extended model and definitions. One-year and median survival for these patients was 81% and 24.0 months, respectively, which is similar to the figures of 82% and 28.6 months observed for the 57 patients classified as favorable by both definitions. Similarly, 50 patients initially classified as intermediate risk are now considered poor risk. One-year and median survival for these patients

Table 6. Multivariable Analysis

Factor	Poor Prognostic Category	Parameter Estimate		
		Mean	SE	*P*
Time from diagnosis to study entry	< 12 months	0.58	0.15	< .001
Hemoglobin	< Lower limit of reference range	0.56	0.14	< .001
Lactate dehydrogenase	> 1.5× upper limit of reference range	0.93	0.23	< .001
Corrected serum calcium	> 10.0 mg/dL	0.71	0.23	< .001
Prior radiotherapy	Yes	0.69	0.18	< .001
Hepatic metastasis	Yes	0.64	0.16	< .001
Lung metastasis	Yes	0.46	0.16	.003
Retroperitoneal node metastasis	Yes	0.32	0.16	.04
Replace individual sites with number of sites*	2 or 3	0.72	0.14	< .001

*Number of metastatic sites based on the presence or absence of metastases to the liver, lung, and retroperitoneal nodes. The parameter estimate is from the model in which number of sites replaces the individual sites.

Table 7. Risk Groups from Motzer et al[13] Model and CCF Extension

Model	Favorable Risk				Intermediate Risk				Poor Risk			
	Patients (%)	Deaths (%)	1-Year Survival (%)	Median Survival (months)	Patients (%)	Deaths (%)	1-Year Survival (%)	Median Survival (months)	Patients (%)	Deaths (%)	1-Year Survival (%)	Median Survival (months)
Motzer et al data, n = 437*	18	74	83	29.6	62	87	58	13.8	20	100	20	4.9
Motzer et al risk groups applied to CCF data, n = 308	19	66	82	28.6	70	83	57	14.6	11	89	16	4.5
CCF risk groups, n = 308†	37	70	81	26.0	35	84	58	14.4	28	89	23	7.3

Abbreviation: CCF, Cleveland Clinic Foundation.
*From Table 7 of Motzer et al.[13]
†Favorable risk includes patients with zero or one poor prognostic factor; intermediate risk includes patients with two poor prognostic factors; and poor risk includes patients with more than two poor prognostic factors present.

were 29% and 8.1 months, respectively, compared with 16% and 4.5 months, respectively, for the 35 patients considered poor risk by both models and 58% and 14.4 months, respectively, for the 107 patients considered intermediate risk by the two models. The similarities in prognosis based on the two models are shown graphically in Figure 2.

Histology and nuclear grade were not considered initially because of the large number of patients for whom this information was not available. However, applying the extended model to the patients for whom histology and nuclear grade were available suggests that histology, but not nuclear grade, may impact on survival. Adjusting for the impact of the prognostic factors included in the extended model, patients with clear-cell tumors had a significantly better prognosis than patients with other histologies ($P = .003$, Fig 3).

DISCUSSSION

This study validates and extends the prognostic model for survival in patients with metastatic RCC proposed by Motzer et al.[13] In addition to confirming the prognostic significance of the patient characteristics and biochemical parameters included in their model, two additional independent prognostic factors were identified. Adjusting for time from initial diagnosis to entry onto the patient's first clinical trial, baseline hemoglobin, serum lactate dehydrogenase, and corrected serum calcium, prior treatment with radiotherapy and the presence of hepatic, lung, and/or retroperitoneal node metastases (or alternatively, the number of metastatic sites) were also identified as independent predictors of poor outcome.

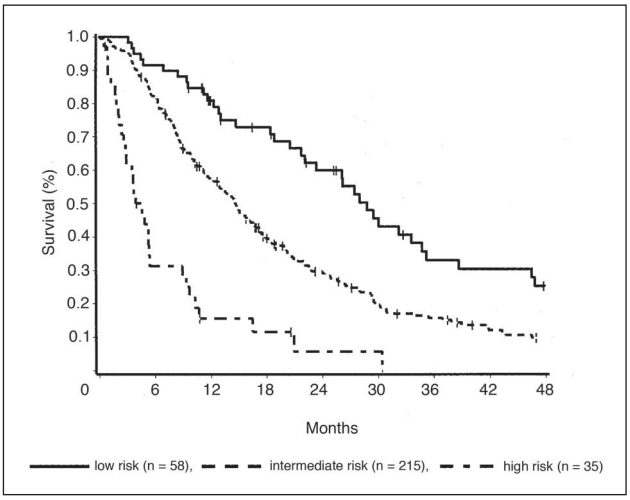

Fig 1. Survival by Motzer et al[13] risk groups.

Although our study validates Motzer et al's model and their criteria for defining risk groups, a difficulty with the model is that the majority of patients are classified as intermediate risk, and relatively few patients are considered as favorable or poor risk. In the present study, 70% of patients were classified as intermediate risk, and only 19% were considered favorable risk. Still fewer patients (11%) were considered poor risk. These proportions are similar to the distribution of risk groups reported by Motzer et al (ie, 18%, 62%, and 20% for favorable, intermediate, and poor risk, respectively). The disproportionately large number of patients in the intermediate risk group suggests that it may be somewhat heterogeneous with respect to outcome.

In the present study, intermediate risk patients with a single poor prognostic factor (n = 99) did have a significantly better prognosis than intermediate risk patients (n = 116) with two poor prognostic factors present ($P = .003$). Extension of the model by incorporating prior radiotherapy and the number of metastatic sites into the definition of risk groups overcomes this difficulty because the expanded definitions essentially reclassify the better prognosis subset of intermediate risk patients as favorable and the poorer prognosis subset as poor risk. This is true even if one separates the intermediate risk group into two subgroups based on whether one or two poor prognostic factors are present. That is, of the 99 patients with one poor prognostic factor based on the original definition, 58 are classified as favorable risk based on the expanded criteria.

Table 8. Comparison of Motzer et al[13] Risk Groups and CCF Risk Groups

Motzer et al Risk Groups	CCF Risk Groups: Favorable Patients (No.)	Favorable 1-Year Survival (%)	Favorable Median Survival (months)	Intermediate Patients (No.)	Intermediate 1-Year Survival (%)	Intermediate Median Survival (months)	Poor Patients (no.)	Poor 1-Year Survival (%)	Poor Median Survival (months)
Favorable	57	82	28.6	1*	—	—	0	—	—
Intermediate	58	81	24.0	107	58	14.4	50	29	8.1
Poor	0	—	—	0	—	—	35	16	4.5

Abbreviation: CCF, Cleveland Clinic Foundation.
*Survival time was 12.2 months.

Median survival time for these patients was 24.0 months, which is similar to the median survival time of 28.6 months observed in the 57 patients who were categorized as favorable risk by both models. Similarly, of the 116 patients with two poor prognostic factors present, 42 are considered poor risk by the expanded criteria. Median survival time for these patients was 8.4 months, which is similar to the median survival time of 4.5 months observed for the 35 patients considered poor risk by both models. One hundred seven patients considered intermediate risk by both models were similar regardless of the number of poor prognostic factors present based on Motzer et al criteria. Median survival time was 14.8 months for the 33 patients with one poor prognostic factor present and 14.4 months for the 74 patients with two poor prognostic factors present.

Another finding in the present study is that, although pathologic features of the primary tumor were often not available, correcting for the factors in the extended model, patients with clear-cell tumors seem to have a significantly better prognosis than patients with other histologies ($P = .003$). Although the proposed extension to the prognostic model proposed by Motzer et al[13] seems to improve the model's discriminatory power and patients with clear-cell tumors seem to have a better prognosis than patients with tumors of other histologies, these results are based on the retrospective analysis of highly selected patients, and confirmation of the results is needed.

In conclusion, six prognostic factors were identified for predicting survival in patients with RCC and most have been validated in different studies. We were able to validate Motzer's data and find additional prognostic factors (prior radiation therapy and number of sites involved) to also be independent prognostic factors in the survival of patients with previously untreated RCC. This can be helpful in refining the definition of intermediate and high risk groups. The good discriminatory power that risk group status seems to have indicates that these are important factors that should be considered in the management of patients with advanced RCC and in the design and analysis of future clinical trials. An international consortium of investigators

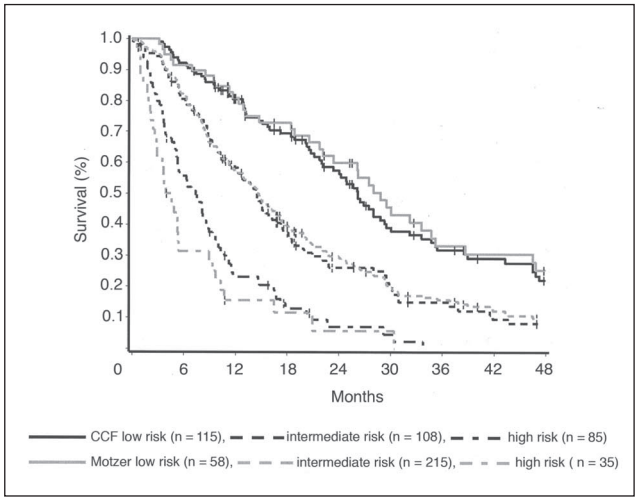

Fig 2. Survival by Motzer et al[13] and Cleveland Clinic Foundation (CCF) risk groups.

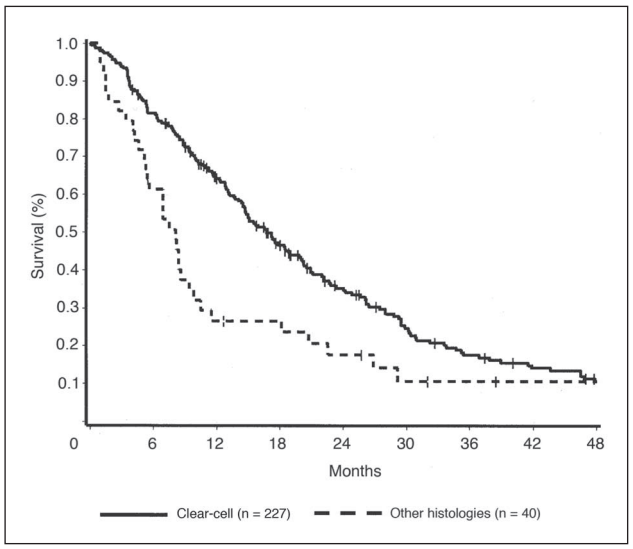

Fig 3. Survival by histology.

has been organized to further examine prognostic factors in patients with metastatic and untreated RCC and to develop a common approach.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant/Advisory Role: Ronald Bukowski, Chiron, Antigenics, Bayer. Honoraria: Ronald Bukowski, Genentech, Amgen, 3M. Research Funding: Ronald Bukowski, Bayer, Genentech. Expert Testimony: Ronald Bukowski, Food and Drug Administration Oncology Advisory Committee. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

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