Yonsei Med J 49(3):451 - 458, 2008
DOI 10.3349/ymj.2008.49.3.451

A Comprehensive Prognostic Stratification for Patients with Metastatic Renal Clear Cell Carcinoma

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Purpose: To develop a reliable prognostic model for patients with metastatic renal cell carcinoma (RCC) based on features readily available in common clinical settings. **Patients and Methods:** A total of 197 patients with RCC who underwent nephrectomy and immunotherapy from 1995 to 2004 were retrospectively reviewed. Their mean age was 55.1 ± 11.8 yrs (24 - 83 yrs) and mean survival time from metastasis was 22.6 ± 20.2 mos (3 - 120 mos). The impact of 24 clinicopathological features on disease specific survival was investigated. **Results:** On univariate analysis, constitutional symptoms, sarcomatoid differentiation, tumor necrosis, multiple primary lesions, liver metastasis, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), thrombocytosis, alkaline phosphatase, hematocrit, T stage, N stage, and nuclear grade had significant influence on survival ($p < 0.05$). Multivariate analysis revealed the following features associated with survival: sarcomatoid differentiation [hazard ratio (HR) = 2.99, $p < 0.001$], liver metastasis (HR = 2.09, $p = 0.002$), ECOG-PS (HR = 1.95, $p = 0.005$), N stage (HR = 1.94, $p = 0.002$), and number of metastatic sites (HR = 1.76, $p = 0.003$). An individual prognostic score was defined as the sum of the weight of these features. According to prognostic scores, patients could be subdivided into 3 groups: low risk (score 0), intermediate risk (score 1 or 2), and high risk (score $\geq$ 3). **Conclusion:** A comprehensive prognostic stratification model was developed to predict survival and stratify patients for prospective clinical trials.

Key Words: Carcinoma, renal cell, neoplasm metastasis, nephrectomy, immunotherapy, prognosis

Received September 28, 2007
Accepted November 27, 2007

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INTRODUCTION

If untreated, the prognosis for patients with metastatic renal cell carcinoma (RCC) is generally poor, with an overall median survival time of no more than 12 mos and a 5-yr survival rate of less than 10%.[1] However, it is not easy to predict the individual prognosis of these patients since the natural history of RCC is complex and influenced by various patient- and tumor-related factors.[2]

Combination therapies of nephrectomy and immunotherapy for patients with metastatic RCC demonstrate only limited benefits.[3,4] Recently, novel molecular-targeted agents showed a significant benefit on progression-free survival in patients for whom cytokine therapy had failed.[5] A variety of important prognostic indicators in metastatic RCC have previously been identified, and several prognosis prediction models have been suggested.[6-12] These models can be used to counsel patients, determine the need for adjuvant therapy, stratify patients for clinical trials, and develop appropriate postoperative surveillance programs to monitor the risk of cancer progression.

In this study, a readily available comprehensive model that is capable of predicting survival of patients with metastatic RCC who underwent radical nephrectomy and immunotherapy in common clinical settings was developed.

PATIENTS AND METHODS

The medical records of 368 patients with histologically proven metastatic RCC from 8 university hospitals were retrospectively reviewed. The cohort was limited to patients who underwent radical nephrectomy and treatment between 1995 and 2004 with at least 1 cycle of immunotherapy [interferon-α, interleukin-2 (IL-2), or a combination thereof with or without 5-flourouracil]. Patients who received other biologic response modifiers and chemotherapeutic regimens were excluded. Exclusion criteria also included non-clear cell histology, von Hippel-Lindau disease, other malignant disease, and followup duration of less than 3 mos. A total of 197 patients were eligible for this study, with 152 males (77.2%) and 45 females (22.8%). Interferon-α monotherapy was performed in 72 patients, IL-2 monotherapy in 9, and combination therapy in 116 patients. The mean age was 55.1 ± 11.8 yrs (range, 24 to 83 yrs) and the mean survival time was 22.6 ± 20.2 mos

Table 1. Patient Characteristics

Characteristics		No. of patients (%)
Gender	Male vs. Female	152 (77.2) vs. 45 (22.7)
Age (yrs)	< 60 vs. ≥ 60	120 (60.9) vs. 77 (39.1)
Constitutional symptoms	Presence vs. Absence	79 (40.1) vs. 118 (59.9)
Local symptoms	Presence vs. Absence	89 (45.2) vs. 108 (54.8)
Laterality	Right vs. Left vs. Bilateral	93 (47.2) vs. 102 (51.8) vs. 2 (1.0)
T stage	T1 - 3 vs. T4	177 (89.8) vs 20 (10.2)
Size (cm)	< 7 vs. ≧ 7	77 (39.1) vs. 120 (60.9)
Nuclear grade	Grade 1 - 3 vs. Grade 4	147 (74.6) vs. 50 (25.4)
Sarcomatoid differentiation	Presence vs. Absence	18 (9.1) vs. 179 (90.9)
Tumor necrosis	Presence vs. Absence	78 (39.6) vs 119 (60.4)
N stage	pNx or pN0 vs. pN1 or pN2	163 (82.7) vs. 34 (17.3)
ECOG-PS	0, 1 vs. 2 - 4	177 (89.8) vs 20 (10.2)
Hematocrit (%)	< 40 vs. ≥ 40	138 (70.1) vs. 59 (29.9)
Platelet count (/mm^3)	< 450,000 vs. ≥ 450,000	175 (90.9) vs. 22 (9.1)
Alkaline phosphatase (U/L)	< 110 vs. ≥ 110	138 (70.1) vs. 59 (29.9)
Aspartate aminotransferase (U/L)	< 40 vs. ≥ 40	179 (89.7) vs. 18 (10.3)
Alanine aminotransferase (U/L)	< 50 vs. ≥ 50	185 (93.9) vs. 12 (6.1)
Calcium (mg/dL)	< 10 vs. ≥ 10	157 (79.7) vs. 40 (20.3)
Timing of metastasis	Concurrent vs. Subsequent	92 (46.7) vs. 105 (53.3)
Number of metastatic sites	< 2 sites vs. ≥ 2 sites	116 (58.9) vs. 81 (41.1)
Lung metastasis	Presence vs. Absence	123 (62.4) vs. 74 (37.6)
Bone metastasis	Presence vs. Absence	66 (33.5) vs. 131 (66.5)
Brain metastasis	Presence vs. Absence	29 (10.3) vs. 253 (89.7)
Liver metastasis	Presence vs. Absence	19 (9.6) vs. 178 (90.4)

ECOG-PS, eastern cooperative oncology group performance status.

(range, 3 to 120 mos). Survival time was defined as the time from diagnosis of metastatic disease to the date of death or last followup.

The impact of various clinicopathological factors on disease-specific survival was investigated. The following patient-related, laboratory, tumor-related, and metastasis-related features were assessed: gender, age, constitutional symptoms at presentation, local symptoms at presentation, Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score, commonly used laboratory tests (hematocrit, platelet, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and calcium level), T stage, tumor size, nuclear grade, sarcomatoid differentiation, tumor necrosis, N stage, timing of metastasis, site of metastatic disease (lung, bone, brain, and liver), and number of metastatic sites. The clinicopathological information of this study cohort is summarized in Table 1.

Table 2. Univariate Analysis for Disease-Specific Survival

		3-yr survival (%)	*p* value*
Gender	Male vs. Female	35.3 vs. 35.7	0.318
Age (yrs)	< 60 vs. ≥ 60	35.4 vs. 36.4	0.588
Constitutional symptoms	Presence vs. Absence	28.9 vs. 40.3	0.035
Local symptoms	Presence vs. Absence	31.2 vs. 39.5	0.048
Laterality	Right vs. Left vs. Bilateral	32.0 vs. 38.3	0.370
T stage	T1 - 3 vs. T4	36.0 vs. 37.5	0.225
Size (cm)	< 7 vs. ≧ 7	39.2 vs. 33.5	0.551
Nuclear grade	Grade 1 - 3 vs. Grade 4	39.0 vs. 25.6	0.016
Sarcomatoid differentiation	Presence vs. Absence	13.9 vs. 38.0	< 0.001
Tumor necrosis	Presence vs. Absence	29.1 vs. 39.9	0.082
N stage	pNx or pN0 vs. pN1 or pN2	39.0 vs. 20.2	0.003
ECOG-PS	0, 1 vs. 2 - 4	39.7 vs. 14.3	0.003
Hematocrit (%)	< 40 vs. ≥ 40	31.9 vs. 43.7	0.106
Platelet count (/mm^3)	< 450,000 vs. ≥ 450,000	37.8 vs. 17.1	0.003
Alkaline phosphatase (U/L)	< 110 vs. ≥ 110	40.6 vs. 24.5	0.036
Aspartate aminotransferase (U/L)	< 40 vs. ≥ 40	36.3 vs. 29.1	0.191
Alanine aminotransferase (U/L)	< 50 vs. ≥ 50	35.8 vs. 32.1	0.465
Calcium (mg/dL)	< 10 vs. ≥ 10	33.6 vs. 45.5	0.381
Timing of metastasis	Concurrent vs. Subsequent	33.8 vs. 37.5	0.388
Number of metastatic sites	< 2 sites vs. ≥ 2 sites	35.4 vs. 24.8	< 0.001
Lung metastasis	Presence vs. Absence	33.4 vs. 39.6	0.283
Bone metastasis	Presence vs. Absence	31.9 vs. 37.8	0.217
Brain metastasis	Presence vs. Absence	10.1 vs. 38.4	0.121
Liver metastasis	Presence vs. Absence	12.3 vs. 38.9	< 0.001

ECOG-PS, eastern cooperative oncology group performance status.
*p value by log-rank test.

Kaplan-Meier curves were generated and compared by using log-rank test for univariate survival analyses. To assess the independent impact of clinicopathological factors on disease-specific survival, Cox proportional hazards regression was used for multivariate survival analyses. Based on rounded regression coefficients [log hazard ratios (HR) in the final Cox model] of variables, the weights of prognostic features were determined. A prognostic score was defined as the sum of the weights of the independent prognostic factors. SPSS for Windows version 12.0 was used for statistical analyses. All p values were 2-sided, and a p value of less than 0.05 was considered to be significant.

RESULTS

Univariate analysis

Of 197 patients, 127 (64.5%) died of cancer at last followup, while 2 (1.0%) died of other causes. The disease-specific survival rate was 65.4% at 1 yr, 35.7% at 3 yrs, and 21.8% at 5 yrs. For univariate analysis, there was no apparent association between survival and gender, age, laterality, T stage, tumor size, tumor necrosis, hematocrit level, liver enzyme level, serum calcium level, timing of metastasis, lung metastasis, bone metastasis or brain metastasis ($p > 0.05$). However, the presence of constitutional symptoms ($p = 0.035$), presence of local symptoms ($p = 0.048$), nuclear grade 4 ($p = 0.016$), presence of sarcomatoid differentiation ($p < 0.001$), nodal involvement ($p = 0.003$), ECOG-PS score of 2 or greater ($p = 0.003$), thrombocytosis ($p = 0.003$), increased alkaline phosphatase ($p = 0.036$), multiple metastatic sites ($p < 0.001$), and presence of liver metastasis ($p < 0.001$) appeared to have a significant influence on survival (Table 2).

Multivariate analysis

Multivariate analysis revealed that the following 5 features were associated with disease-specific survival: sarcomatoid differentiation (presence vs. absence, HR = 2.99, $p < 0.001$), liver metastasis (presence vs. absence, HR = 2.09, $p = 0.002$), ECOG-PS (≥ 2 vs < 2, HR = 1.95, $p = 0.005$), N stage (≥ 1 vs 0, HR = 1.94, $p = 0.002$), and number of metastatic sites (≥ 2 vs 1, HR = 2.024, $p = 0.003$) (Table 3).

Prognostic stratification model

The weights of independent prognostic factors were defined as follows: sarcomatoid differentiation was given a weight of 2, and the remaining

Table 3. Multivariate Analysis for Disease-Specific Survival

	HR	95% CI	p value*	Weight
Constitutional symptoms	1.36	0.94 - 1.95	0.099	-
Local symptoms	1.31	0.90 - 1.91	0.153	-
ECOG-PS	1.95	1.22 - 3.12	0.005	0 vs. 1
Platelet count	1.34	0.74 - 2.41	0.333	-
Alkaline phosphatase level	1.24	0.84 - 1.83	0.276	-
N stage	1.94	1.27 - 2.99	0.002	0 vs. 1
Nuclear grade	1.03	0.65 - 1.64	0.899	-
Sarcomatoid differentiation	2.99	1.72 - 5.21	< 0.001	0 vs. 2
Liver metastasis	2.09	1.32 - 3.33	0.002	0 vs. 1
Number of metastatic sites	1.76	1.22 - 2.53	0.003	0 vs. 1

HR, hazard ratio; CI, confidence interval; ECOG-PS, eastern cooperative oncology group performance status score.
*p value by multivariate Cox proportional hazard model.

Table 4. Disease-Specific Survival Rates by Risk Group

Risk group	Cumulative risk score	Patients (n)	Median time to death (mos)	Disease-specific survival rate (%)		
				1 yr	3 yrs	5 yrs
Low	0	70	44	80.8	55.4	36.0
Intermediate	1 or 2	97	18	66.9	29.2	17.1
High	≥ 3	30	6	24.3	0.0	0.0
Total		197	20	65.4	35.7	21.8

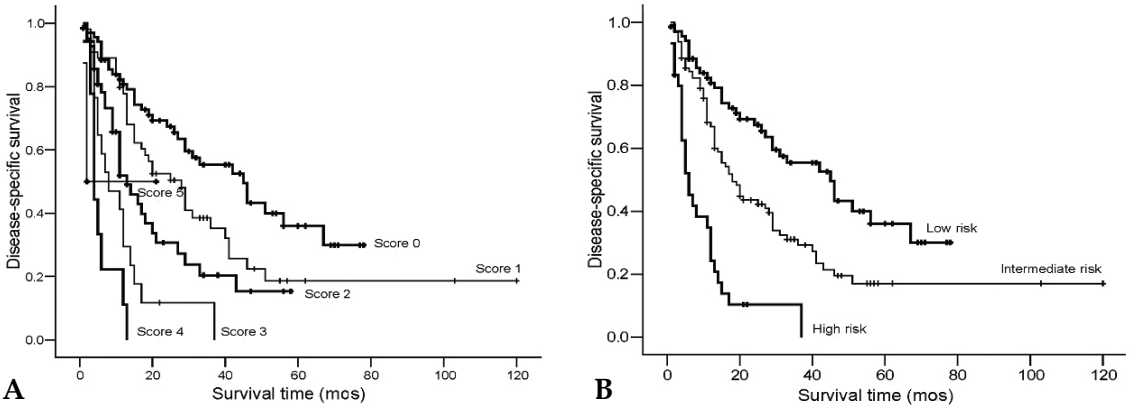

Fig. 1. Disease-specific survival curves according to risk scores (A) and risk groups (B). p value = 0.001 between low risk and intermediate risk, p value < 0.001 between intermediate risk and high risk.

4 factors were assigned a weight of 1 (Table 4).

An individual prognostic score was defined as the sum of the weights of these factors. The prognostic scores were 0 in 70 patients, 1 in 55, 2 in 42, 3 in 17, 4 in 9, and 5 in 4. Survival curves showed a statistically significant difference between those with scores 0 and 1 (p = 0.038) and scores 2 and 3 (p = 0.039). However, there was no difference between those with scores 1 and 2 (p = 0.052), 3 and 4 (p = 0.061), and 4 and 5 (p = 0.618) (Fig. 1).

As a consequence, the cohort was subdivided into 3 groups as follows: a low risk group (score 0), intermediate risk group (score 1 or 2), and high risk group (score 3 or greater) (Fig. 1), each of which had disease-specific survival rates that are shown in Table 4.

DISCUSSION

Investigators have concentrated on the prognostic stratification of patients with advanced or metastatic RCC for years, and a number of RCC outcome prediction models have previously been reported.[6-12] Zisman et al. reported a single predictive system of patients with and without metastatic RCC, the University of California Los Angeles Integrated Staging System (UISS), which is based on 661 patients and incorporates TNM pathologic stage, ECOG-PS, and Fuhrman grade to predict overall survival after patients undergo radical nephrectomy. Frank et al.[13] proposed the stage, size, nuclear grade, and necrosis (SSIGN) score, which is based on 1801 patients with clear cell RCC treated by radical nephrectomy. The SSIGN score stratifies the risk of death from RCC based on these features.

Recently, prognostic prediction systems have focused only on metastatic RCC.[6-10] Motzer et al.[10] suggested the prognostic stratification of 670 patients with advanced RCC. In their study, 5 prognostic factors (Karnofsky performance status,

serum lactate dehydrogenase, hemoglobin, corrected serum calcium, and prior nephrectomy) were identified and used to categorize patients with metastatic RCC into 3 risk groups. They also reviewed 463 patients who were treated with interferon-α for metastatic RCC and developed another algorithm that consists of Karnofsky performance status, lactate dehydrogenase, hemoglobin, corrected serum calcium, and time from diagnosis to immunotherapy.[9] Leivobich et al.[8] proposed the first predictive algorithm in patients with metastatic RCC after nephrectomy and IL-2-based immunotherapy. In their model, regional lymph node status, constitutional symptoms, location of metastases, sarcomatoid histology, and thyroid stimulating hormone (TSH) levels were associated with survival. Atzpodien et al.[6] demonstrated a comprehensive prognostic system of pretreatment clinical parameters in patients with metastatic RCC treated with different subcutaneous recombinant cytokine-based home therapies in consecutive trials. Six parameters (neutrophil counts, lactate dehydrogenase, C-reactive protein, time from diagnosis of tumor to metastatic disease, number of metastatic sites, and bone metastasis) were identified as independent prognostic factors.

In our study, 24 clinicopathological features were evaluated for their impacts on survival of patients with metastatic RCC who were treated with nephrectomy and immunotherapy. Subsequently, a new comprehensive prognostic model was devised that consisted of 3 risk groups. The study data showed various median survival times according to each risk group ranging from 6 mos in the high-risk group to 44 mos in the low-risk group. This scoring system was determined by the weighted sum of 5 features (sarcomatoid differentiation, liver metastasis, ECOG-PS, N stage, and number of metastatic sites). The weight of each variable was considered and only sarcomatoid differentiation was given a weight of 2 because of its strong prognostic impact (HR = 2.99). The relatively strong impact of sarcomatoid differentiation has also been identified in previous reports.[8,11]

Generally, extrapulmonary metastasis has been regarded as an independent prognostic factor in metastatic RCC patients.[7,8,14,15] In this study, only hepatic involvement showed a significant influence on survival whereas brain and bone involvement did not. Although the cut-off value to define multiplicity of metastatic sites has been inconsistent, many authors have emphasized the significance of the number of metastatic sites in these patients.[6,7,16-18] Performance status was established as an important prognostic factor without any uncertainty,[9,10,16-19] suggesting a prognostic significance for regional node involvement similar to the work of Leibovich et al. However, it is not certain whether regional nodal involvement is a feasible prognostic factor in any metastatic RCC patients since both this study and those of Leibovich et al. are restricted to patients who underwent nephrectomy and immunotherapy.

The present study was limited to patients with clear cell RCC since the histological subtype is associated with the biologic aggressiveness of RCC.[20] To eliminate possible confounding factors, the study cohort was limited to patients with metastatic RCC who were treated with nephrectomy and immunotherapy. Nevertheless, the study still showed some limitations as well as the general limitations of a retrospective study, where immunotherapy protocol and number of cycles were not identical, and this difference was not considered in the data analysis. However, systemic immunotherapy demonstrated a minimal impact on outcome in advanced RCC, suggesting that the difference did not cause a significant bias in developing this prognostic model.

The objectives of this study were to develop a reliable prognostic model based on features readily available to clinicians and pathologists. There are no other ancillary tests such as erythrocyte sedimentation rate, thyroid stimulating hormone, C-reactive protein, and lactate dehydrogenase that have previously been studied and identified as useful in the management of patients with RCC.[6,8-10,14,15] For this reason, the clinical feasibility of this model is expected to be greater in common clinical settings. Recently, race has been shown to be a significant predictor of overall survival within a clinical trial patient population with RCC, even in those with metastatic RCC.[21,22] However, there was no literature in English about a predictive model for patients treated with nephrectomy and immunotherapy based on Asian

populations including Koreans. Therefore, the prognostic model described herein can be used to predict survival and stratify patients for prospective clinical trials although further validation of the model through prospectively designed clinical trials is needed.

In summary, sarcomatoid differentiation, liver metastasis, ECOG-PS, N stage, and number of metastatic sites were found to be independently associated with survival of patients with metastatic RCC who were treated with nephrectomy and immunotherapy. Based on these features, a comprehensive prognostic stratification model was developed to predict survival and stratify patients for prospective clinical trials.

ACKNOWLEDGEMENTS

We wish to thank the other members of the Severance Urologic Oncology Group: Yun Seob Song, and Won Jae Yang, Soonchunhyang University; Hong Sup Kim, Konkuk University; Young-Sig Kim, National Health Insurance Corporation Ilsan Hospital; Sun Il Kim, Ajou University; Sang Hyeon Cheon, Ulsan University; Joong Shik Lee, Sungkyunkwan University; and Ki Hak Song, Konyang University.

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