



Prognostic factors associated with the response to sunitinib in patients with metastatic renal cell carcinoma

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ABSTRACT

Objective

We investigated the prognostic clinicopathologic factors associated with overall survival (OS) and progression-free survival (PFS) in the once-daily continuous administration of first-line sunitinib in a consecutive cohort of Turkish patients with metastatic renal cell carcinoma (RCC).

Methods

The study enrolled 77 Turkish patients with metastatic RCC who received sunitinib in a continuous once-daily dosing regimen between April 2006 and April 2011. Univariate analyses were performed using the log-rank test.

Results

Median follow-up was 18.5 months. In univariate analyses, poor PFS and OS were associated with 4 of the 5 factors in the Memorial Sloan-Kettering Cancer Center (MSKCC) score: Eastern Cooperative Oncology Group performance status of 2 or higher, low hemoglobin, high corrected serum calcium, and high lactate dehydrogenase. In addition to those factors, hypoalbuminemia, more than 2 metastatic sites, liver metastasis, non-clear cell histology, and the presence of sarcomatoid features on pathology were also associated with poor PFS; and male sex, hypoalbuminemia, prior radiotherapy, more than 2 metastatic sites, lung metastasis, nuclear grade of 3 or 4 for the primary tumour, and the presence of sarcomatoid features were also associated with poorer OS. The application of the MSKCC model distinctly separated the PFS and OS curves ($p < 0.001$).

Conclusions

Our study identified prognostic factors for PFS and OS with the use sunitinib as first-line metastatic RCC

therapy and confirmed that the MSKCC model still appears to be valid for predicting survival in metastatic RCC in the era of molecular targeted therapy.

KEY WORDS

Metastatic renal cell carcinoma, prognostic factors, sarcomatoid features, first-line therapy, vascular endothelial growth factor, VEGF antagonist

1. INTRODUCTION

Metastatic renal cell carcinoma (RCC) has historically been resistant to chemotherapy and hormonal therapy. Immunotherapy has been used as a first-line treatment in advanced or metastatic RCC with limited success. However, the treatment of metastatic RCC has changed dramatically with the availability of new treatment options. Molecular research into the pathogenesis of RCC has provided valuable information about the altered signalling pathways in RCC, including that of vascular endothelial growth factor (VEGF) and its receptor¹. Molecularly targeted therapies were specifically developed to target these signal transduction pathways. Clinical trials have demonstrated a survival benefit for targeted agents, particularly in clear cell RCC patients². However, metastatic RCC progresses in all patients, resulting in a critical need to determine patient risk and to optimize treatment.

Sunitinib is an orally administered, multi-targeted receptor tyrosine kinase inhibitor^{3,4}. A prospective randomized phase III clinical trial of systemic treatment in untreated metastatic RCC patients has demonstrated the superiority of sunitinib over interferon with respect to objective response rate, progression-free survival (PFS), and overall survival (OS)^{2,5}. An acceptable safety profile for sunitinib was also shown. In the first Turkish study conducted in metastatic RCC patients, we found that response rates and tolerability with continuous once-daily administration of sunitinib were comparable to those

observed in earlier randomized studies⁶. The results of previous studies also demonstrated that sunitinib is widely used in the first- or second-line settings in metastatic RCC in Turkey.

The natural history of metastatic RCC is quite variable. The role of factors that predict outcomes is therefore an important consideration in the evaluation and development of new treatment strategies. In this era of VEGF-targeted therapies, new prognostic variables are required for clinical trial design, patient counselling, and risk-directed therapy. Currently, the most widely used prognostic model comes from the Memorial Sloan–Kettering Cancer Center (MSKCC). The model developed at MSKCC classifies risk in RCC patients as favourable, intermediate, or poor according to the number of factors that predict survival⁷. Although the MSKCC model was independently validated by investigators at the Cleveland Clinic⁸ and used for the study and interpretation of cytokine and targeted drug therapies, it is important to note that the prognostic risk profiles were derived during the era of immunotherapy and were limited to a population of patients eligible for participation in immunotherapy-based clinical trials. In addition, a question commonly asked by clinicians is whether RCC patients in clinical trials are representative of the RCC patients seen in ordinary clinical practice. Many patients with RCC, particularly those with poorer prognoses, do not meet trial inclusion criteria. Thus, new prognostic profiles with updated survival data are needed to reflect the current treatment paradigm for patients with metastatic RCC.

The aim of the present study was therefore to investigate the prognostic clinicopathologic factors associated with OS and PFS in the once-daily continuous administration of first-line sunitinib delivered using an institutional treatment protocol in a consecutive cohort of Turkish patients with metastatic RCC.

2. METHODS

2.1 Patient Population

Our study enrolled 77 patients with histologically verified metastatic RCC who were treated with sunitinib between April 2006 and April 2011. Patient data were collected from a consecutive prospective patient series at the Institute of Oncology, Istanbul University, Istanbul, Turkey. Demographics and clinicopathologic characteristics—including age, sex, RCC histologic subtype, Eastern Cooperative Oncology Group (ECOG) performance status (PS), sites of metastasis, laboratory findings, and patient survival—were recorded from charts. In all RCC patients, the diagnosis was based on a histologic analysis of specimens obtained by radical nephrectomy or ultrasonography-guided needle biopsy. All available slides were retrieved and reviewed by a single expert genitourinary pathologist (IK).

Patients were included in the study independent of histologic subtype. Patients with an ECOG PS of 4 and those with severe concomitant medical illnesses were excluded. All patients received sunitinib as first-line systemic treatment on an outpatient basis. Sunitinib was administered at a once-daily dose of 37.5 mg. Treatment cycles were repeated every 4 weeks without interruption between cycles unless participants experienced disease progression or severe toxicity. A dose reduction of sunitinib (to 25 mg) was allowed depending on the type and severity of adverse events. Treatment was discontinued in patients with progression or severe toxicity after dose reduction. Thyroid dysfunction and arterial hypertension were managed with appropriate medication without dose reduction.

Each patient was classified according to the MSKCC risk scoring system at the beginning of the treatment period⁷. Computed tomography or magnetic resonance imaging was performed at baseline and every third treatment cycle to assess clinical response according to the Response Evaluation Criteria in Solid Tumors, version 1.0⁹.

The local institutional review board approved the study, and all patients provided written informed consent before participating. The study met the requirements of the Declaration of Helsinki.

2.2 Statistical Analysis

The prognostic variables investigated in our analysis were based on a general review of pretreatment features. The OS was calculated from the date of the first dose of sunitinib to either the date of death, the date of the final follow-up visit, or the study end date. The PFS was calculated from the date of the first dose of sunitinib to the date of death from any cause or to disease progression as defined by the Response Evaluation Criteria in Solid Tumors.

Survival curves were estimated using the Kaplan–Meier method, and the log-rank test was used to compare curves. All baseline factors were examined as binary variables. Each variable was investigated using a univariate analysis for OS and PFS. Multivariate analysis was not performed because of the limited sample size and the low number of outcome events. All *p* values represent 2-sided tests of statistical significance, with *p* < 0.05 being considered statistically significant. The SPSS software application (version 16.0: SPSS, Chicago, IL, U.S.A.) was used for the statistical analyses.

3. RESULTS

3.1 Clinical Features

The median patient age was 58 years (range: 26–80 years), and the 77 patients included 50 men (65%)

and 27 women (35%). The diagnosis in 68 patients (88%) was clear cell RCC; the others were diagnosed with papillary ($n = 8$) or chromophobe ($n = 1$) RCC. According to the MSKCC risk scoring system, 19% of the patients were classed as favourable-risk ($n = 15$); 53%, as intermediate-risk ($n = 41$); and 27% as poor-risk ($n = 21$). Most of the patients ($n = 68$, 88%) had already undergone nephrectomy. Metastectomy, including lung and retroperitoneal areas, had been performed in 17 patients (22%). The most frequent sites of metastasis were lung (49 patients, 64%), lymph nodes (36 patients, 47%), bone (31 patients, 40%), liver (15 patients, 19%), and brain (8 patients, 10%).

3.2 Patient Outcome

The median treatment duration was 10 months (range: 2–42 months), with 26% of patients achieving a confirmed partial response; 3%, a complete response; and 48%, stable disease. The remaining 23% of patients experienced disease progression. At the time of the present analysis, 42 patients had developed disease progression, and 28 patients had died.

3.2.1 Survival Analyses

Median follow-up was 18.5 months (range: 2–43 months). At study end, 47 patients (64%) were alive, and 2 patients had been lost to follow-up. Estimated median PFS and OS were 13 months (95% confidence interval: 5.6 to 20.4 months) and 25 months (95% confidence interval: 18.7 to 31.2 months) respectively.

Median PFS stratified by MSKCC risk status was 28, 21, and 6 months for favourable-, intermediate-, and poor-risk patients respectively ($p < 0.001$, Figure 1). Median OS time was not reached for the favourable-risk group, 25 months for the intermediate-risk group, and 9 months for the poor-risk group ($p < 0.001$, Figure 2).

3.2.2 Univariate Analysis of Risk Factors for PFS and OS

Table 1 presents all 21 covariates, with their univariate analyses. In the MSKCC score, 4 of the 5 factors—ECOG PS of 2 or greater, low hemoglobin, high corrected serum calcium, and high lactate dehydrogenase (LDH)—were associated with poor PFS and OS. In addition to those factors, hypoalbuminemia, more than 2 metastatic sites, liver metastasis, non-clear cell histology, and presence of sarcomatoid features on pathology were also associated with poor PFS. Nuclear grade, prior radiotherapy, and lung metastasis did not appear to have an impact on PFS. The PFS was also unaffected by sex, age, platelet count, neutrophil count, creatinine, time from diagnosis to current treatment, nephrectomy, and bone or brain metastasis. Male sex, hypoalbuminemia, prior radiotherapy, more than 2 metastatic sites,

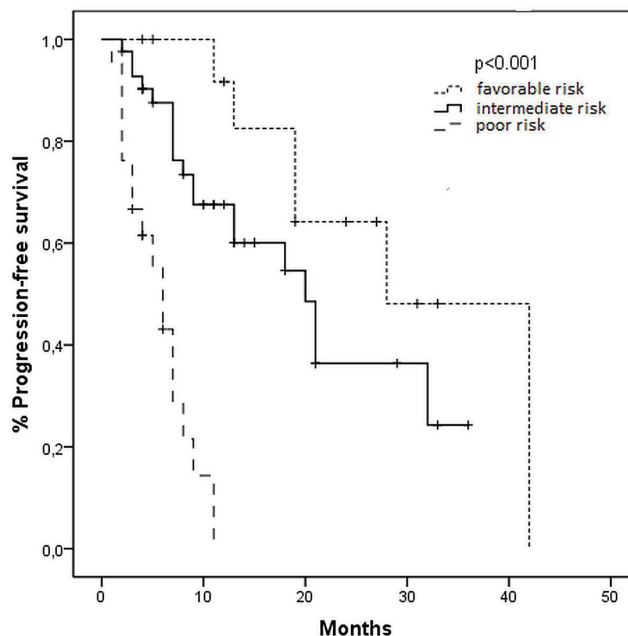


FIGURE 1 Kaplan–Meier curves for progression-free survival in patients treated with sunitinib, by risk group (Memorial Sloan–Kettering Cancer Center criteria).

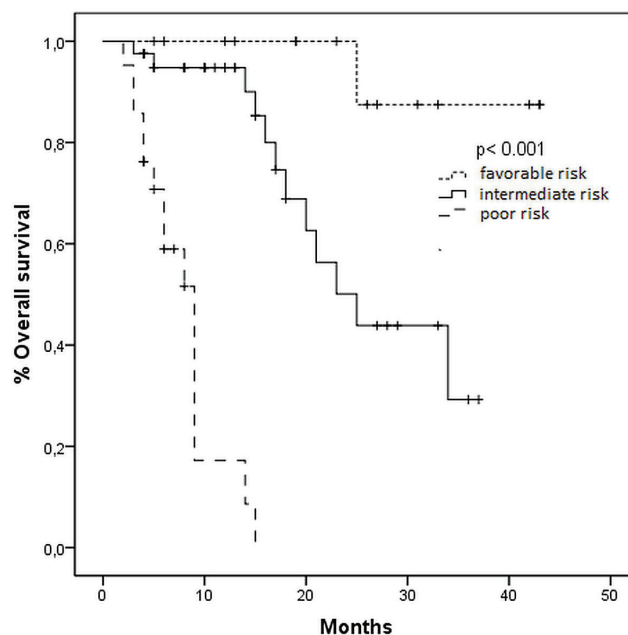


FIGURE 2 Kaplan–Meier curves for overall survival in patients treated with sunitinib, by risk group (Memorial Sloan–Kettering Cancer Center criteria).

lung metastasis, nuclear grade 3 or 4 of the primary tumour, and presence of sarcomatoid features were also associated with poorer OS. Nephrectomy and non-clear cell histology had a borderline significant impact on OS. Notably, no other factors were associated with differences in OS.

TABLE 1 Univariate analyses of survival by clinicopathologic and laboratory covariates

Characteristic	Pts (n)	Overall survival (months)		p Value	Progression-free survival (months)		p Value
		Median	95% CI		Median	95% CI	
Clinicopathologic features							
ECOG performance status							
0–1	56	34	12.5 to 44.2	<0.001	20	17.1 to 22.8	
≥2	19	9	7.3 to 10.6		7	4.5 to 9.4	
Sex							
Men	50	23	15.1 to 30.9	0.014	11	0.0 to 22.9	0.50
Women	27	NR	—		18	10.6 to 25.3	
Age							
>60 Years	30	34	14.2 to 53.7	0.3	13	0.0 to 29.3	0.47
≤60 Years	47	23	15.1 to 30.8		18	9.1 to 26.9	
Time from Dx to systemic treatment							
≤1 Year	50	34	10.7 to 57.2	0.95	13	1.7 to 24.8	0.74
>1 Year	24	23	16.6 to 29.8		18	8.6 to 27.4	
Prior radiotherapy							
Yes	24	15	8.2 to 21.7	0.045	9	6.2 to 11.7	0.06
No	21	25	16.7 to 33.2		21	10.9 to 31.1	
Nephrectomy							
Yes	68	23	17.1 to 28.8	0.099	18	11.1 to 24.9	0.54
No	9	34	0.0 to 76.8		8	0.3 to 15.6	
Number of metastatic sites							
≤2	46	34	14.4 to 53.5	0.029	18	9.8 to 28.1	0.04
>2	30	25	9.7 to 40.2		7	1.9 to 12.0	
Lung metastasis							
Yes	49	18	11.9 to 24.1	0.01	11	6.1 to 15.9	0.07
No	28	NR	—		28	9.9 to 46.1	
Liver metastasis							
Yes	15	21	7.8 to 34.1	0.15	7	3.9 to 10.0	0.02
No	62	25	14.1 to 35.9		19	11.1 to 26.9	
Bone metastasis							
Yes	31	17	6.2 to 27.7	0.21	11	0.0 to 22.1	0.47
No	46	25	16.5 to 33.4		18	10.9 to 25.3	
Brain metastasis							
Yes	8	18	8.3 to 27.6	0.15	9	3.9 to 14.1	0.16
No	69	34	17.1 to 50.0		18	8.8 to 27.2	
Grade							
1–2	13	NR	—	0.039	20	6.6 to 33.4	0.07
3–4	58	20	14.1 to 25.8		11	7.2 to 14.7	
Histology							
Clear cell	67	25	13.1 to 36.8	0.081	19	9.2 to 28.7	0.04
Non-clear cell	10	15	2.9 to 27.1		7	1.3 to 12.6	

PROGNOSTIC FACTORS FOR METASTATIC RCC

TABLE 1 Continued

Characteristic	Pts (n)	Overall survival (months)		p Value	Progression-free survival (months)		p Value
		Median	95% CI		Median	95% CI	
Sarcomatoid							
Without	56	NR	—		20	12.6 to 27.3	
With	21	9	7.2 to 10.8	<0.001	7	4.1 to 9.8	0.01
MSKCC risk group							
Favourable	15	NR	—		28	9.9 to 46.0	
Intermediate	41	25	21.2 to 28.7	<0.001	21	12.1 to 29.9	0.01
Poor	21	9	7.4 to 10.5		6	4.1 to 7.8	
Laboratory data							
Hemoglobin ^a							
Normal	51	NR	—		19	11.1 to 26.9	
Anemia	26	23	5.7 to 40.2	0.015	7	4.2 to 9.7	0.006
Corrected calcium ^b							
>10 mg/dL	12	9	2.6 to 15.4		7	6.1 to 7.9	
≤10 mg/dL	63	34	19.5 to 48.5	0.006	19	10.6 to 27.3	0.03
Lactate dehydrogenase ^c							
≥1.5×ULN	7	9	4.8 to 13.2		7	0.0 to 19.8	
<1.5×ULN	68	25	18.8 to 31.2	0.006	19	10.6 to 27.4	0.01
Neutrophil count ^d							
≥ULN	23	15	7.9 to 22.0		9	3.6 to 14.3	
<ULN	51	34	19.6 to 48.4	0.16	19	10.6 to 27.4	0.30
Platelet count ^e							
≥ULN	19	23	0.0 to 52.6		19	5.5 to 32.5	
<ULN	56	25	17.8 to 32.1	0.3	13	4.9 to 21.1	0.50
Creatinine							
≥1.5 mg/dL	11	17	13.9 to 20.1		13	0.4 to 25.5	
<1.5 mg/dL	62	25	14.1 to 35.8	0.36	19	8.2 to 29.7	0.12
Albumin							
≥4 g/dL	31	34	19.8 to 48.2		19	7.4 to 30.5	
<4 g/dL	17	14	4.7 to 23.2	0.016	8	4.8 to 11.2	0.05

^a Lower limits of reference range: men, 13.0 g/dL; women, 11.5 g/dL.

^b Reference range was 8.3–10.7 mg/dL. Corrected calcium = measured total Ca (mg/dL) + 0.8 [4.0 – serum albumin (g/dL)].

^c Upper limit of reference range: 450 U/L.

^d Upper limit of reference range: 7.7×10³/mm³.

^e Upper limit of reference range: 450×10³/mm³.

Pts = patients; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group performance status; NR = not reported; Dx = diagnosis; MSKCC = Memorial Sloan-Kettering Cancer Center; ULN = upper limit of normal.

4. DISCUSSION

In the present analysis, we assessed prognostic factors affecting OS and PFS in a series of 77 RCC patients treated with continuous daily sunitinib. In contrast with studies that used anti-VEGF treatments,

our study cohort was homogenous, and all patients received sunitinib as first-line treatment^{10–12}. Additionally, patients were enrolled into the study consecutively, accurately reflecting current clinical practice in advanced RCC. Median PFS (13 months) and OS (25 months), and the objective response

rate (29%) in our patient cohort were found to be comparable with the results of previously reported randomized studies (11 and 26 months, 4 months, and 31% respectively)².

Therapies targeting VEGF have created a new environment for clinical trial development and patient care involving patients with metastatic RCC. Prognostic and predictive models are required to adequately stratify patients in clinical trials, to provide relevant clinical information to patients receiving therapy, and to facilitate risk-directed treatment selection in clinical practice¹³. For example, sunitinib or bevacizumab plus interferon alfa have been cited as the preferred treatment options for metastatic RCC patients with favourable- or intermediate-risk features¹⁴. In contrast, temsirolimus has been recommended as a preferred treatment option for RCC patients with poor-risk features, because of a large phase III trial that was directed primarily to that patient population¹⁵. A biologic surrogate marker that predicts a favourable response to a targeted agent is preferred before a patient receives that agent. Currently, validated markers do not exist, although certain positive associations have recently been published^{16–18}. Until such markers are prospectively validated, patient selection will rely on the baseline clinicopathologic characteristics of candidates for targeted therapies.

One of the most widely used predictive models for patients with metastatic RCC is the MSKCC system developed by Motzer *et al.*, which categorizes patients into favourable-, intermediate-, and poor-risk groups according to number of adverse factors, a time from diagnosis to start of systemic therapy of less than 1 year, elevated serum LDH, high corrected serum calcium, anemia, and low performance status. In 2005, Makhail *et al.*⁸ suggested several modifications to the “2002 Motzer score” variables, such as the addition of prior exposure to radiotherapy and of variables indicating the presence of nodal, hepatic, and lung metastases. In 2009, a large retrospective study by Heng *et al.*¹⁰ of prognostic factors for OS in patients receiving VEGF-targeted agents devised and internally validated a model that replicates the Motzer methodology and relies on 4 of the 5 Motzer criteria (hemoglobin, corrected calcium, Karnofsky PS, and time from diagnosis to treatment) in addition to neutrophil and platelet counts. Other recent data from Patil *et al.*¹³ were prospectively obtained from patients treated with first-line sunitinib or interferon alfa in a phase III clinical trial. For sunitinib, a multivariate analysis of PFS identified 5 independent predictors: serum LDH, presence of 2 or more metastatic sites, no prior nephrectomy, ECOG PS, and baseline platelet count. By contrast, a multivariate analysis of OS identified serum LDH, corrected serum calcium, time from diagnosis to treatment, hemoglobin, ECOG PS, and presence of bone metastasis as predictors.

In our study, laboratory parameters (hypoalbuminemia, anemia, hypercalcemia, and high LDH), histopathologic data (high nuclear grade, non-clear cell histology, and presence of sarcomatoid features on pathology), more than 2 metastatic sites, and poor ECOG PS were associated with adverse outcomes. Karnofsky PS, anemia, LDH elevation, and hypercalcemia are factors that have previously been reported in the MSKCC criteria and that might reflect any or all of increased tumour burden, aggressive tumour biology, or paraneoplastic processes^{8,19,20}. Furthermore, neutrophilia and thrombocytosis might be markers of inflammation related to the overproduction of cytokines resulting from increased tumour burden or aggressive tumour biology^{21,22}. However, our study did not reveal any association between those variables and survival.

The prognostic role of metastasis localization was also evident. Outcomes were improved in metastatic RCC patients with pulmonary metastasis, but PFS was inferior in patients with hepatic metastasis. Bone and brain metastasis had no effect on prognosis. Factors that are traditionally included—such as time from diagnosis to current treatment and nephrectomy status—were not found to be informative in the present study. Nearly all the patients included in our study had already had a nephrectomy. The median OS and PFS of the entire patient cohort (25 and 13 months respectively)—and of the patient strata with favourable (OS: not reached; PFS: 28 months), intermediate (OS: 25 months; PFS: 21 months), and poor prognosis (OS: 9 months; PFS: 6 months)—are longer than those seen in earlier studies from the era of immunotherapy^{2,7}.

In the present study, sarcomatoid differentiation was associated with short and inferior PFS and OS. Metastatic RCC with sarcomatoid differentiation is also associated with poor outcomes after chemotherapy or immunotherapy. In a recent study that included patients who had sarcomatoid RCC, the clinical response to VEGF-targeted agents compared favourably with responses to chemotherapy or immunotherapy in earlier studies²³. The same study also suggested that outcomes with anti-VEGF therapy were better in patients with underlying clear cell histology than in those with non-clear cell sarcomatoid metastatic RCC. Further validation of the suggestion that sarcomatoid differentiation is a negative prognostic indicator for OS is required.

One limitation of our study is that the sample was relatively small and came from a single oncology centre in Turkey, which limits the generalizability of the results. In addition, the sample was drawn from a heterogeneous population: just 9 patients had non-clear cell carcinoma. This study also did not address or investigate the prognostic value of molecular markers for RCC. Prospective investigation of clinical and molecular features in a large number of patients with RCC will be required. Future

studies performing similar evaluations of patients with metastatic RCC in other countries are needed.

5. CONCLUSIONS

The MSKCC prognostic factors appear to retain their validity for predicting survival in metastatic RCC in the era of molecular targeted therapy. Continued progress in the identification of patient-specific prognostic factors for metastatic RCC will require further advances in the knowledge of tumour-specific biology.

6. ACKNOWLEDGMENTS

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7. CONFLICT OF INTEREST DISCLOSURES

The authors declare that they have no financial conflicts of interest.

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