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Research Article

Evaluation of Factors Influencing Survival in Metastatic Renal Cell Cancer

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Abstract

Objectives: The use of prognostic factors that can correctly predict the clinical outcomes of patients with mRCC has particular importance for individualized risk assessment. In this study, we aimed to address the prognostic factors in mRCC patients.

Methods: Eighty-six patients who were diagnosed with de-novo metastatic renal cell cancer or developed metastasis during follow-up between January 2007-January 2020 were included and their files were retrospectively evaluated. From patient files; demographic characteristics [age, gender, EGOC PS (Eastern Cooperative Oncology Group performance status), tumor localization, tumor size, metastasis status, metastatic sites], histopathological characteristics and laboratory tests (hemoglobin, serum albumin, lactate dehydrogenase), treatments they received were recorded.

Results: Factors determined to be significant in univariate analysis were assessed using multivariate analysis and the results identified a tumor size larger than 6 cm (p= 0.032), ECOG PS ≥2 (p< 0.001), a hemoglobin level below 13 gr/dl (p= 0.016) and a serum albumin level below 3.6 gr/dl (p= 0.006) as independent unfavorable prognostic factors associated with overall survival.

Conclusion: Our study determined tumor size>6cm, hemoglobin ≤13gr/dL, serum albumin ≤3,6 gr/dL and ECOG PS ≥2 as factors influencing the prognosis unfavorably in mRCC patients.

Keywords: Metastatic renal cell cancer, prognostic factors, hypoalbuminemia

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Renal cell carcinoma (RCC) is the most prevalent solid renal tumor and accounts for 87% of all renal cancers.[1] It is a common malignancy that is estimated to result in 403.000 new annual cases and 175.000 deaths worldwide.[2] RCC constitutes 5% of all cancers in males and 3% of all cancers in females.[3] Curative intervention with surgical resection (partial or radical nephrectomy) is the standard treatment method for patients with clinically localized RCC.[4] Following curative treatment for localized RCC, 30% of the patients show recurrence.[5] The prognosis is poor once distant metastasis occurs.[6] The use of prognostic factors that can correctly predict the clinical outcomes of patients with metastatic RCC (mRCC) has particular importance for individualized risk assessment.[7] The TNM classification assesses the anatomical extent of the tumor and it is the best indicator of the prognosis in RCC. Five-year survival rates are above 90% in stage I, 75-95% in stage II and 59-70% in stage III. In stage 4, a median overall survival of 28 months has been achieved by administering targeted therapies.[8] Apart from the stage, scoring systems associated with the

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prognosis have been developed. The most widely used risk scoring systems are the Memorial Sloan Kettering Cancer Center (MSKCC) system and the risk scoring system developed by the International Metastatic RCC Database Consortium (IMDC).[9,10] Patients are stratified into risk groups based on these scoring systems and individualized treatment decisions are made. Although the parameters included in the MSKCC and IMDC scoring indices are involved in the recommended models, some studies have revealed that there may be other prognostic factors besides these. In this study, we aimed to investigate the effects of parameters that are easily accessible in routine practice on the prognosis.

Methods

Data of 135 patients who presented to the Medical Oncology Clinic of Dicle University, Faculty of Medicine due to renal cell cancer between January 2007-January 2020 were retrospectively evaluated. The study was approved by the Dicle University Medical Faculty Ethics Committee (25.02.2021-124). All of the ethical considerations had been strictly followed in accordance with the Helsinki declaration. Data of 86 patients who either presented with de-novo metastasis or relapsed after resection during follow-up were acquired and these patients were enrolled.

Patients aged 18 years or older with a histopathologically confirmed renal cell cancer diagnosis who were either denovo metastatic or developed metastasis during follow-up were included in the study.

From patient files; demographic characteristics (age, gender, EGOC PS, smoking, tumor localization, tumor size, nephrectomy status, metastasis status, metastatic sites), histopathological characteristics, laboratory findings (hemoglobin, creatinine, serum albumin, lactate dehydrogenase), treatments they received were recorded.

For univariate and multivariate analyses, 13 variables that could influence overall survival were selected based on previous studies. The variables identified were as follows: age (<65 years or ≥65 years), gender (female or male), smoking exposure (yes or no); nephrectomy (yes or no), metastatic sites (liver, bone and lung), histopathological subtype (clear cell, sarcomatoid, papillary and chromophobe type), localization (right or left), tumor size (large or small), ECOG PS (0-1 or 2), first-line treatment (sunitinib, pazopanib, sorafenib and everolimus), hemoglobin (normal or low), serum albumin (normal or low) and LDH (normal or high).

SPSS 18.0 statistics software package was used to analyze the data obtained in this study. Overall survival (OS) was defined as the time from the date of diagnosis to the date of last examination or death from any cause. Descriptive parameters were presented as median values in a 95% confidence interval. We used descriptive statistics in order to evaluate patient characteristics and the frequency of parameters, student's t-test for normally distributed numerical data, Mann-Whitney-U test for the analysis of non-parametric variables. A ROC analysis was performed to determine the optimal cut-off value for certain variables that could be associated with survival. Survival analysis (OS) was conducted using Kaplan-Meier analysis. The Cox regression test was used for multivariate analyses. The level of significance was accepted as $p<0.05$.

Results

This study included a total of 86 patients diagnosed with metastatic renal cell carcinoma, of whom 21 (24.4%) were female and 65 (75.6%) were male. Patients' median age at diagnosis was 54.2 (range; 25-81) years. Sixty-six patients were histopathologically diagnosed by performing nephrectomy and 20 (23.3%) by performing tru cut biopsy. According to the TNM classification, 38 (44.2%) of the patients were de-novo metastatic at diagnosis while 48 (55.8%) developed metastasis later. Laboratory results obtained at diagnosis were as follows: hemoglobin (gr/dl) 13 (7-20), platelet count (103/microL) 265 (63-627), creatinine (mg/dL) level 1 (0,4-9), serum albumin (gr/dL) level 3,7 (1,5-4,9), lactate dehydrogenase (LDH) (U/L) 206 (102-880). At the time of data analysis, 64 of the patients (74.4%) had died, while 22 (25.6%) were still alive. General characteristics of the patients are described in detail in Table 1.

The ROC analysis conducted to determine the optimal cut-off values for the parameters that could be associated with survival found cut-off values of 13 gr/dl for hemoglobin (68% sensitivity, 50% specificity, AUC=0.648, p=0.040), 3,6 gr/dl for serum albumin (86% sensitivity, 54% specificity, AUC=0.737, p=0.001), 6 cm for tumor size (78% sensitivity, 50% specificity, AUC=0.671, p=0.018).

Median follow-up duration in our study was 32 (1-152) months. Univariate analysis determined undergoing nephrectomy (33 months vs. 19 months, p= 0.032), tumor size (47 months vs. 26 months, p= 0.021), ECOG PS (33 months vs. 8 months, p<0.001), hemoglobin level (39 months vs. 13 months, p=0.015) and serum albumin level (28 months vs. 13 months, p>0.001) as prognostic factors associated with OS. Factors determined to be significant in univariate analysis were assessed using multivariate analysis and the results identified a tumor size larger than 6 cm (HR: 1.87, 95% CI 1.05-3.33, p= 0.032), ECOG PS ≥2 (HR: 4.15, 95% CI 2.02-8.51, p< 0.001), hemoglobin level below 13 gr/dl (HR: 0.49, 95% CI 0.28-0.87, p=0.016) and a serum albumin level

Table 1. Demographic and Clinical Characteristics of Patients

	Value n (%)
Age (years) (median, range)	54.4 (25-81)
Gender	
Female	21 (24.4)
Male	65 (75.6)
Smoker	
Yes	64 (74.4)
No	22 (25.6)
Tumor localization	
Right kidney	50 (50)
Left kidney	50 (50)
Tumor size (median, range) (cm)	7 (2-21)
Nephrectomy	
Yes	66 (76.7)
No	20 (23.3)
Histological subtype	
Clear cell	70 (81.4)
Papillary	9 (10.5)
Chromophobe	3 (3.5)
Sarcomatoid	2 (2.3)
Others	2 (2.3)
Metastasis status	
Metastatic at diagnosis	38 (44.2)
Later developing metastasis	48 (55.8)
Location of metastases	
Lung	57 (63.3)
Bone	38 (44.2)
Liver	11 (12.8)
Others	13 (15.1)
ECOG PS (no)	
0-1	71 (82.6)
≥2	15 (17.4)
Heamoglobin (median, range) (gr/dL)	13 (7-20)
>13gr/dL	37 (43.1)
≤13gr/dL	49 (56.9)
Creatinine (median, range) (mg/dL)	1 (0.4-9)
LDH (median, range) (U/L)	206 (102-880)
Albumin (median, range) (gr/dL)	3.7 (1.5-4.9)
>3.6 gr/dL	37 (43.1)
≤3.6gr/dL	49 (56.9)
First line treatment	
Sunitinib	54 (62.8)
Pazopanib	24 (27.9)
Sorafenib	5 (5.8)
Evorilimus	3 (3.5)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; LDH: Lactate dehydrogenase.

below 3.6 gr/dl (HR: 0.46, 95% CI 0.26-0.81, p= 0.006) as independent unfavorable prognostic factors associated with overall survival. Table 2 and Table 3 present the results of univariate and multivariate analyses.

Discussion

This retrospective study was conducted to investigate the effects of parameters that are easily accessible in routine practice on the prognosis. Although mRCC used to be associated with a median overall survival of around 10-15 months, median survival has surpassed two years with the use of novel therapies [targeted therapies, immunotherapy]. Many patients show disease recurrence caused by local recurrence and distant metastases. However, the absence of an optimal surveillance strategy and consensus as to the prognostic biomarkers counters disease management.[11,12,13] Thus, the identification of reliable and precise prognostic biomarkers is gradually becoming more important. The classical anatomical prognostic factor is the tumor, lymph node and metastasis (TNM) classification, which has been the most commonly used staging system for years.[14] TNM includes various prognostic properties such as tumor size, invasion of the venous system, invasion of the collecting system, extension to the adrenal gland, invasion beyond the renal capsule or Gerota fascia (T classification) and spread to regional lymph nodes and distant regions (N and M classification). In all RCC subtypes, the prognosis worsens with a more advanced TNM classification.[15]

Although the primary tumor size is an important predictor of the outcome in patients with localized disease, its role in the prognosis of mRCC has not been clearly explored.[16] In a study conducted by DiNatale RG. and colleagues, mRCC patients were classified as those with a primary tumor size larger than 4 cm and those with a primary tumor size smaller than 4 cm, and the patient group with a tumor size smaller than 4 cm was shown to have a longer survival.[17] In RCC, there is a correlation between tumor diameter and stage, with 5-year survival rates declining as the tumor diameter increases (particularly ≥10 cm). It has been shown previously that tumor size alone is an independent prognostic factor.[18] Siddiqui and colleagues reported 10-year cancer-specific survival rates of 77%, 54% and 46% in T3a tumors for the tumor sizes ≤4 cm, 4-7 cm, >7 cm, respectively.[19] In our study, median OS was 47 months in patients with a tumor size ≤6 cm and 26 months in those with a tumor size >6 cm. A primary tumor size >6 cm was associated with a short survival and this corroborated the literature.

It was observed that the patients' prognoses vary and that some show longer survival times. Accordingly, pre-treatment prognostic factors that are correlated with a longer survival have been revealed. Numerous clinical prognostic factors including performance status (PS), presence of symptoms, paraneoplastic syndromes and laboratory values such as calcium, serum albumin, hemoglobin and C-reactive protein (CRP) have been investigated. The Me-

Table 2. Factors affecting survival results of univariate and multivariate analysis

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Age	1.01	0.99-1.03	0.19			
Gender	0.92	0.52-1.61	0.77			
Smoker	1.13	0.63-2.02	0.67			
Nephrectomy (yes/no)	1.85	1.05-3.25	0.032	1.20	0.63-2.29	0.56
Metastasis status at baseline	1.23	0.74-2.02	0.41			
Liver metastasis	1.00	0.47-2.13	0.98			
Lung metatasis	1.00	0.59-1.71	0.98			
Bone metastasis	1.10	0.67-1.81	0.69			
Histological subtype			0.76			
Clear cell type		reference				
Sarkomatoid type	0.83	0.11-6.05	0.85			
Papillary type	1.43	0.61-3.35	0.40			
Chromophobe type	0.65	0.15-2.69	0.55			
Localization	1.19	0.72-1.95	0.48			
Tumor size (cm) (>6/≤6)	1.91	1.10-3.32	0.021	1.87	1.05-3.33	0.032
ECOG PS(0-1/≥2)	3.69	2.02-6.73	<0.001	4.15	2.02-8.51	<0.001
First line treatment			0.79			
Pazopanib		reference				
Sunitinib	1.11	0.62-1.99	0.71			
Evorilimus	0.76	0.17-3.35	0.72			
Sorafenib	3.62	1.29-10.1	0.014			
Heamoglobin gr/dL (>13/≤13)	0.53	0.31-0.88	0.015	0.49	0.28-0.87	0.016
Serum albumin gr/dL (>3,6/≤3,6)	0.39	0.23-0.64	<0.001	0.46	0.26-0.81	0.005
LDH(U/L)	1.00	0.99-1.00	0.44			

ECOG PS: Eastern Cooperative Oncology Group Performance Status; LDH: Lactate dehydrogenase; HR: Hazard ratio; CI:confidence interval.

Table 3. Survival results by researched factors

	OS (months)	HR	95% CI	p
Overall survival	28 (20-36)			
Nephrectomy		1.85	1.05-3.25	0.032
Yes	33 (21.8-44.1)			
No	19 (8.1-29.8)			
Tumor size (cm)		1.91	1.10-3.32	0.021
≤6	47 (17.2-76.7)			
>6	26 (16.2-35.7)			
ECOG PS		3.69	2.02-6.73	<0.001
0-1	33 (26.2-39.7)			
≥2	8 (1-18)			
Heamoglobin (gr/dl)		0.53	0.31-0.88	0.015
>13	39 (18.8-59.1)			
≤13	13 (2.7-23.2)			
Serum albumin (gr/dL)		0.39	0.23-0.64	<0.001
>3,6	28 (19.9-36.0)			
≤3,6	13 (7-18.9)			

ECOG PS: Eastern Cooperative Oncology Group Performance Status; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.

morial Sloan Kettering Cancer Center (MSKCC) score, which makes use of five factors including the time from diagnosis to systemic treatment, Karnofsky performance score, hemoglobin, LDH and calcium levels, determined the median OS as 30 months for patients in the favorable risk group, 14 months for patients in the intermediate risk group, and 5 months for patients in the poor risk group.[10] The International Metastatic RCC Database Consortium (IMDC) specified six prognostic factors for patients receiving targeted therapy that consist of the time from diagnosis to systemic treatment, Karnofsky performance score, hemoglobin, calcium, neutrophil count and platelet count. The patients are stratified into three groups based on the number of risk factors. Median OS was determined as 43.2 months in the favorable risk group, 22.5 months in the intermediate risk group and 7.8 months in the poor risk group.[20] In these two large studies, poor performance status was an unfavorable risk factor; similarly, our study determined that a poor performance status was associated with a short survival and that the median OS was 33 months in patients with a PS of 0-1 as opposed to 8 months in patients with a

PS ≥2 (p<0.001). As is the case in other cancers, we reason that a poor performance status also has a negative impact on survival in RCC since it hampers treatment effectiveness and continuation.

A contribution to survival was demonstrated in mRCC patients who received systemic treatment after cytoreductive nephrectomy; in a prospective study conducted by The Southwest Oncology Group (SWOG) that compared patients who received IFN after cytoreductive nephrectomy and patients who only received interferon (IFN) without cytoreductive surgery, the OS was longer in patients who received IFN after nephrectomy (11.1 months, 8.1 months, respectively, p=0.012).[21] In the study performed by the European Organisation for Research and Treatment of Cancer (EORTC), an improvement was determined in progression-free survival and overall survival in patients who received IFN after nephrectomy.[22] In retrospective studies conducted by the IMDC and the National Cancer Database regarding patients receiving targeted therapy, cytoreductive surgery prior to systemic treatment was determined to improve OS.[23,24] However, in the CARMENA study conducted on patients in the intermediate and poor risk groups, in which sunitinib therapy was used, median OS was longer in patients who used sunitinib alone than in patients who used sunitinib after nephrectomy (23.4 months versus 19 months in the intermediate risk group, 13.3 months versus 10.2 months in the poor risk group).[25] In our study, median OS was 33 months in patients who underwent nephrectomy and 19 months in those who did not, in support of the SWOG and EORTC studies. However, our study was not consistent with the CARMENA study. This may be because patients in the CARMENA study were in the intermediate and poor risk groups.

Anemia was detected in 29-88% of mRCC patients.[26] In our patients, anemia was found at a rate of 56.9%. In the study Negrier S. and colleagues conducted on 782 patients diagnosed with mRCC; hemoglobin <11.5 g/dL (female), <13 g/dL (male), ECOG PS ≥1, nephrectomy (yes) were determined to be linked to poor survival.[27] In the study by Chrom and colleagues, 266 patients who received first-line tyrosine kinase inhibitor (TKI) therapy were evaluated and this study reported that anemia, hypercalcemia and high LDH had a negative effect on the OS.[28] Similarly, our study determined a median OS of 39 months in patients with a hemoglobin level >13 gr/dL and 13 months in patients with a hemoglobin level ≤13 gr/dL (p=0.015). Downs T.M. and colleagues also found in their study that that anemia, thrombocytosis, serum calcium levels, weight loss, patient's performance status, metastatic site and number of metastases were significant factors indicating the prognosis in the metastatic condition.[29]

The serum albumin level is widely used as an indicator of the nutritional status.[30] Morgan and colleagues showed that nutritional deficiency (BMI <18,5 kg m2, serum albumin <3,5 g/dl or pre-operative weight loss ≥%5 weight loss) was linked to poor survival in RCC patients who were surgically treated.[31] Corcoran and colleagues revealed that hypoalbuminemia was associated with a poor OS in mRCC patients.[32] Further, malnutrition indicated by hypoalbuminemia was reported to be related to an immunosuppressed state.[33] In our study, median OS was 13 months (≤3.6 gr/dL) in patients with hypoalbuminemia as opposed to 28 months in those without hypoalbuminemia (>3.6 gr/dL) (p<0.001). Low serum albumin levels were associated with a short survival, in agreement with the literature. We reason that the low serum albumin levels in metastatic patients arise from malnutrition.

Conclusion

In our study, low hemoglobin, low serum albumin levels, tumor size >6 cm, and ECOG Performance Status ≥2 were determined to be unfavorable independent prognostic markers associated with survival. As an addition to the IMDC and MSKCC scoring systems used in predicting the prognosis, this study also determined tumor size and hypoalbuminemia as factors associated with the prognosis. The use of these parameters that are also associated with the prognosis, which are more easily accessible in clinical practice, in addition to the existing scoring systems will be effective for the clinician in predicting the prognosis and regarding the treatment decision.

Disclosures

Ethics Committee Approval: The study was conducted based on the rules of Declaration of Helsinki and approved by the Institutional Ethics Committee of Dicle University, Faculty of Medicine (Document number: 25.02.2021-124).

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