http://dx.doi.org/10.5272/jimab.2016221.1045

Journal of IMAB
ISSN: 1312-773X
http://www.journal-imab-bg.org

Journal of IMAB - *Annual Proceeding (Scientific Papers)* 2016, vol. 22, issue 1

# PROGNOSTIC FACTORS FOR SURVIVAL IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA TREATED WITH CHEMOTHERAPY

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**ABSTRACT:**

**Objective:** The aim of this study was to investigate the prognostic significance for survival of certain clinical and pathological factors in patients with advanced or metastatic renal cell carcinoma (mRCC) treated with chemotherapy.

**Methods:** From 1990 to 2009 sixty seven consecutive patients with mRCC, treated in UMHAT- Dr. G. Stranski, *Department of Medical Oncology* entered the study. Parameters including some patients characteristics, hematological and pathological parameters, were evaluated for their role as predictors of overall survival. The therapeutic regimens included Interferon- alpha or Medroxyprogesterone acetat. Survival analysis was evaluated by Kaplan- Meier test. The influence of pretreatment characteristics as prognostic factor for survival was analyzed using multivariate stepwise Cox regression analyses.

**Results:** Variables significantly associated with overall survival univariate analysis were performance status> 1, thrombocytosis, anemia and number of metastatic sites > 1. In multivariate analysis as independent poor prognostic factors were identified poor performance status and multiple sites of metastasis.

**Conclusion:** These results indicated that performance status, presence of elevated platelet counts or anemia as well as well as multiple site of metastasis could be useful prognostic factors in patients with mRCC.

**Key words:** Prognostic factors, Metastatic renal cell carcinoma, Survival

## INTRODUCTION

In the United States, renal cell carcinoma (RCC) accounts for 2%- 3% of the cancer incidence and 2% of the cancer mortality. There were 65150 new cases of kidney and renal pelvis cancers and 13680 cancer- related deaths in the United States (1). Due to the rareness of warning signs, 25-30% of the patients presents with metastatic disease at the time of diagnosis. Approximately 50% of patients treated with nephrectomy develop metastases subsequent to surgery (2). The majority of these patients need systemic therapy. Despite recent therapeutic advances, responses rates with biologic and immunologic therapies are low at 15- 25% with median survival under two years and five year survival rate of less than 10% (3).

The natural history of mRCC is quite variables, and therefore an important consideration in the evaluation and development of new treatment strategies is the role of factors that are predictive of outcome. Use of known prognostic factors can help direct therapies to patients groups most likely to benefit from them and can help identify patients for which watchful waiting is a suitable alternative, thus potentially preserving alternatives for later use.

Several patient- or tumor- related parameters have been identified as prognostic factors in patients with mRCC. Among these are absence or presence of nephrectomy, baseline hemoglobin (Hb), baseline lactate dehydrogenase, alkaline phosphatase (AP), location and number of metastasis, Karnofsky performance status (4). A model derived from Memorial Sloan- Kettering Cancer Center (MSKCC) was based on a study of 670 patients treated during clinical trials between 1975 and 1996 (5). Five variables were selected by univariate and multivariate analysis as prognostic, and were used as risk factors for short survival: low Karnofsky performance status (< 80%), high lactate dehydrogenase (> 1,5 X upper limit of normal), low serum Hb (less than the lower limit of normal), high corrected serum calcium (>2,62 mmol/L), and absence of prior nephrectomy. Currently, the choice of the most appropriate algorithm for treatment of patients with mRCC is an unresolved question (6).

The aim of this study was to investigate the prognostic significance for survival of certain clinical and pathological factors in patients with mRCC treated with chemotherapy.

## PATIENTS AND METHODS

A retrospective study was conducted to investigate the possible prognostic factors of RCC. We reviewed the medical records of patients with RCC treated for metastatic disease in UMHAT- Dr. G. Stranski, *Department of Medical Oncology*, during the period 1990- 2010. Patients had histologically confirmed RCC and were treated surgically with nephrectomy when possible and had clinical or biopsy evidence of metastatic disease with at least one measurable lesion. Assessment of extend of disease consisted of chest radiography, abdomen ultrasound and, if necessary, computer tomography of the thorax and bone scans was performed. Treatment schedule consisted of interferon- alpha 3 mln UI s.c. three times per week or medroxyprogesterone acetate 500 mg per os once daily until progression of disease or inappropriate toxicity.

Recorded clinical features included age, gender, World health organization (WHO) performance status, Hb level, leukocyte count, platelet count, AP, serum calcium. Fifty- four years and younger at diagnosis was defined as young patients. Anemia was defined as Hb <120 g/L in men and <110 g/L in women. Thrombocytosis was defined as a platelet count of > $400x10^9$/L. Elevated AP was defined higher than 280 UI/L. All patient with serum calcium higher than 2, 62 mmol/L were considered as hypercalcaemic.

Pathologic features was determined from the pathologist's reports. Parameter assessed included histology type of RCC (clear- cell versus non- clear- cell type), site of metastasis and number of metastasis.

Follow- up information, including cause of death, was ascertained through a review of clinical notes. Overall survival (OS) was recorded and correlated with the above clinical, hematological and pathological parameters.

OS was measured from the time at the start of chemotherapy treatment to the death.

All sixty seven patients were included in the statistical calculations. The OS was estimated by the method of Kaplan and Meier (7). Variables were studied for influence on survival in a univariate analysis by using the log- rank test, and in a multivariate analysis using the Cox proportional hazard regression analysis (8). The results were considered statistically significant at the p< 0, 05 levels.

## RESULTS

A total of 67 patients with mRCC, treated with chemotherapy from January 1990 till December 2009 were analysed regardless of their length of treatment. All patients had undergone chemotherapy consisting of interferon- alpha or medroxyprogesterone acetate. Baseline demographic and disease characteristics are summarized in Table 1. The median age of patients was 62,7 years (range 39- 76 years) and 54% of patients were >60 years. The male/ female ratio was 71,6% to 28,4%. The most of the patients were in good WHO- performance status (0-1- 69,2%, 2-3- 30,8%). The most common histology type was clear cell carcinoma- 54 patient (80,6%), the patients with other histology were 13 (19,4%). The most common metastatic location was the bone (46,2%) and the lung (35,9%). Most of the patients were with one number of metastatic sites at presentation (67,2%). The median follow- up period was 10 months (4- 28 months). Hb was found as normal in 48 patients (71,6%) and 19 patients (28,4%) were with anemia. Leukocyte and platelet count were normal in 43 (64,1%) and 49 (73,2%) of patients, respectively. Serum calcium and AP were elevated in 12 (17,9%) and 26 (38,8%) of patients, respectively.

The median OS was 11 months (range 1- 22) months. The following pre- treatment factors were identified as univariate predictors of poor survival (Table 2): WHO performance status >1, elevated platelet counts ≥$400x10^9$/L, anemia with Hb level <120 g/L in men and <110 g/L in women and number of metastatic sites > 1.

In contrast, no statistically significant differences were found for the following parameters: age, sex, histological type, metastatic location other than bone, AP level, leukocyte count, and serum calcium.

Two factors were found to be significant in multivariate analysis. As shown in Table 3, the major unfavorable prognostic factors were performance status at presentation >1 and multiple number of metastasis.

## DISCUSSION

Classical prognostic factors for non- metastatic RCC include anatomical, histological, clinical, and some molecular features. Kattan et al. were the first authors to develop a nomogram to predict the probability of RCC recurrence after nephrectomy (9). Currently, the most commonly used prognostic models for localized RCC are the University of California Los Angeles integrated staging system (UISS) and the 'Stage, Size, Grade, and Necrosis' (SSIGN) developed at the Mayo Clinic. UISS predicts patient survival by integrating the TNM stage, Fuhrman's grade, and ECOG performance status, while SSIGN calculates prognostic score according to stage, size, grade, and necrosis (10,11). The use of prognostic indicators might play a crucial role in predicting outcome and adopting new adjuvant treatments to the needs of individual patients. Patient profiling and assigning into risk categories is an important concept as it allows prediction of tumor behavior and, therefore, patient prognosis (12). Additionally, it allows the selection of the most suitable therapeutic option for each of them (13).

The aim of our study was to define the relationship between some clinical, laboratory and pathological characteristics and survival in patients with advanced or metastatic RCC. To achieve this goal, 67 patients treated with chemotherapy were analyzed with respect to survival.

Multivariate analysis of the data identified multiple sites of metastasis and poor performance status to be the most important predictors of survival. These results are in agreement with findings from other investigators. The prognostic factors vary among the studies but consistently include performance status and a measure of extent of disease. The study of Elson et al. contained patients with mRCC, treated with chemotherapy between 1975 and 1984. The model stratified patients into five categories with a difference in median survival time of as little as 1,3 months between groups and identify as main prognostic factors performance stetus, number of metastatic sites and time from initial diagnosis and prior cytotoxic therapy (14). Motzer et al. analyzed patients with mRCC too and defined among main prognostic factors performance status, elevated lactate dehydrogenase and low Hb level (6). Leibovich at al considered that main prognostic factors are locations of metastases, lymphatic node invasion and gender (15). In the last two studies the patients multiple sites of metastasis or poor performance status were with unfavorable prognosis. In a large metaanalysis Negrier et al. find nine prognostic factors for survival in 782 patients with mRCC, treated by cytokines. These independent factors with a high degree of significance (p<0,01) were biologic signs of inflammation, time interval from renal tumor to metastases, presence of bone metastasis, presence of liver metastasis, ECOG performance status, elevated neutrophil count, elevated level of AP, multiple number of metastatic sites and low HB level (16).

The main limitations of the present study are inherent to its retrospective nature and the relatively small number of patients. We also could not study some biological prognostic factors (such as C- reactive protein, lactate dehydrogenase or erythrocyte sedimentation rate) because of the lack of data. Prognostic factors that can risk stratify patients, predictive biomarkers that can help individualize treatment selection and predict a patient's response to therapy, facilitate the better understanding and treatment of the disease (17). Despite their adequate prognostic ability, none of the established prognostic models is 100% accurate. In consequence, the search for more accurate markers continues. Molecular events that can unveil the biologic heterogeneity underlying the varied clinical behavior of mRCC may help improve individualized prognostication and risk-stratified clinical decision making (18). Novel prognostic factors and more up-to-date models are urgently needed for patients with metastatic RCC, especially in the era of targeted therapies (19).

## CONCLUSIONS

Our findings confirm the potential role of some clinicopathological and hematological parameters as predictive tools of mRCC. Prognostic models should widely be used in the clinical practice to counsel patients, plan surveillance protocols, and select appropriate candidates for inclusion in adjuvant treatment protocols. Further improvements in our ability to predict RCC prognosis will rely on the integration of molecular and genetic markers in the currently established models.

**Table 1.** Baseline patient's characteristics

| Characteristics | Number of patients- 67 |
|---|---|
| Age (years) | 48 - 77 |
| Sex | |
| Male | 48 (71,6%) |
| Female | 19 (28,4%) |
| Histological type | |
| Clear cell | 54 (80,6%) |
| Papillary | 9 (13,4%) |
| Chromophobe | 3 ( 4,5%) |
| Collecting duct | 1 (1,5%) |
| Performance status WHO | |
| 0 | 36 (53,8%) |
| 1 | 11 (16,4%) |
| 2 | 14 (20,9%) |
| 3 | 6 (8,9%) |
| Site of metastasis | |
| Lung | 24 (35,9%) |
| Liver | 9 (13,4%) |
| Bone | 31 (46,2%) |
| Others | 3 (4,5%) |
| Number of metastatic sites | |
| 1 | 45 (67,2%) |
| >1 | 22 (32,8%) |
| Hemoglobin level | |
| Normal | 48 (71,6%) |
| Low | 19 (28,4%) |
| Leukocyte count | |
| Normal | 43 (64,1%) |
| Elevated | 24 (35,9%) |
| Platelet count | |
| Normal | 49 (73,2%) |
| Elevated | 18 (26,8%) |
| Alkaline phosphatase | |
| Normal | 41 (61,2%) |
| Elevated | 26 (38,8%) |
| Serum calcium | |
| Normal | 55 (82,1%) |
| Elevated | 12 (17,9%) |

**Table 2.** Results of univariate survival analysis.

| Factor | Favorable | Unfavorable | HR | 95% CI | P- value |
|---|---|---|---|---|---|
| Age | <65 | ≥65 | 1,12 | 0,48 -1,23 | NS |
| Gender | Female | Male | 1,23 | 0, 76-1,45 | NS |
| Performance status | 0-1 | 2-3 | 1,36 | 1,12 -1,88 | <0,001 |
| Histology type | Clear cell | Others | 1,09 | 0,86 -1,45 | NS |
| Platelet count | $<400x10^9$/L | $\geq400x10^9$/L | 1,58 | 1,14 - 2,23 | <0,001 |
| Alkaline phosphatase | Normal | Elevated | 1,23 | 0,96- 1,55 | NS |
| Serum calcium | Normal | Elevated | 1,18 | 0,88-1,47 | NS |
| Leukocyte count | Normal | Elevated | 1,38 | 1,01-1-88 | NS |
| Hemoglobin level | Normal | Anemia | 1,78 | 1,23-2,49 | <0,001 |
| Number of metastasis | 1 | >1 | 1,37 | 1,12-2,24 | <0,001 |
| Site of metastasis | Bone | Others | 1,25 | 0,91-2,13 | NS |

HR- Hazard ratio, CI- Confidence interval, NS-Not significant

**Table 3.** Results of multivariate survival analysis.

| Factor | Favorable | Unfavorable | HR | 95% CI | P-value |
|---|---|---|---|---|---|
| Performance status | Others | 2 | 1,53 | 1,17 -2,12 | <0,001 |
| Platelet count | $<400x10^9$/L | $\geq400x10^9$/L | 1,22 | 0,89- 1,53 | NS |
| Hemoglobin level | Normal | Anemia | 1,31 | 0,98 -1,69 | NS |
| Number of metastasis | 1 | Others | 1,76 | 1,22- 2,33 | <0,001 |

HR- Hazard ratio, CI- Confidence interval, NS- Not significant

**REFERENCES:**


1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin*. 2013 Jan-Feb;63(1):11-30. [CrossRef]

2. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, et al. EAU guidelines on renal cell carcinoma: the 2010 update. *Eur Urol.* 2010 Sep;58(3):398-406. [PubMed] [CrossRef]

3. Lam JS, Shvarts O, Leppert JT, Figlin RA, Belldegrun AS. Renal cell carcinoma 2005: new frontiers in staging, prognostication and targeted molecular therapy. *J Urol.* 2005 Jun; 173(6):1853-1862. [PubMed] [CrossRef]

4. Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2004 Feb;22(3):454-463. [PubMed] [CrossRef]

5. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol*. 1999 Aug;17(8):2530-2540. [PubMed]

6. Ficarra V, Novara G, Galfano A, Brunelli M, Cavalleri S, Martignoni G, et al. The 'Stage, Size, Grade and Necrosis' score is more accurate than the University of California Los Angeles Integrated Staging System for predicting cancer- specific survival in patients with clear cell renal cell carcinoma. *BJU Int,* 2009 Jan;103(2):165-170. [PubMed] [CrossRef]

7. Kaplan EL, Meier P, Non-parametric estimation from incomplete observations. *J Am Stat Assoc,* 1959; 53:457-481.

8. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observations in each patient II. Analysis and examples. *Br J Cancer.* 1977 Jan;35(1):1-39. [PubMed]

9. Kattan MW, Reuter V, Motzer RJ, Katz J, Russo P. A postoperative prognostic nomogram for renal cell carcinoma. *J Urol.* 2001 Jul;166(1):63-67. [PubMed] [CrossRef]

10. Zisman A, Pantuck AJ, Wieder J, Chao DH, Dorey F, Said JW, et al. Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. *J Clin Oncol.* 2002 Dec;20(23):4559-66. [PubMed] [CrossRef]

11. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An

outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: The SSIGN score. *J Urol.* 2002 Dec;168(6):2395-400. [PubMed] [CrossRef]

12. Leppert JT, Pantuck AJ, Figlin RA, Belldegrun AS. The role of molecular markers in the staging of renal cell carcinoma. *BJU Int.* 2007 May; 99(5 Pt b):1208-11. [PubMed] [CrossRef]

13. Brassart E, Lebdai S, Berger J, Traore S, Bernhard JC, Fardoun T, et al. Overall mortality after radical nephrectomy in patients aged over 80 years with renal cancer: A retrospective study on preoperative prognostic factors. *Int J Urol.* 2012 Jul;19(7):626-32. [PubMed] [CrossRef]

14. Elson PJ, Witte RS, Trump DL. Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. *Cancer Res.* 1988 Dec;48(24 Pt 1):7310-13. [PubMed]

15. Leibovich BC, Cheville JC, Lohse CM, Zincke H, Frank I, Kwon ED, et al. A scoring algorithm to predict survival for patients with metastatic clear cell carcinoma: a stratification tool for prospective clinical trials. *J Urol.* 2005 Nov;174(5):1759-63. [PubMed] [CrossRef]

16. Negrier S, Escudier, Douilard J-Y, Ravaud A, Buclon M, Perol D. et al. Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: a report from the Groupe Fransais d'Immunoterapie. *Ann Oncol.* 2002 Sep;13(9):1460-68. [PubMed] [CrossRef]

17. Finley DS, Pantuck AJ, Belldegrun AS. Tumor biology and prognostic factors in renal cell carcinoma. *Oncologist.* 2011; 16(Suppl 2):4-13. [PubMed]

18. Sun M, Shariat SF, Cheng C, Ficarra V, Murai M, Oudard S, et al. Prognostic Review. *Eur Urol.* 2011 Oct;60(4):644-661. [PubMed] [CrossRef]

19. Sun M, Shariat SF, Karakiewicz PI. Factors affecting outcome in renal cell carcinoma. *Curr Opin Urol.* 2010 Sep;20(5):355-360. [PubMed] [CrossRef]

*Please cite this article as:* Davidov D. Prognostic Factors for Survival in Patients with Metastatic Renal Cell Carcinoma Treated with Chemotherapy. *J of IMAB.* 2016 Jan-Mar;22(1):1045-1049.
DOI: http://dx.doi.org/10.5272/jimab.2016221.1045

Received: 30/11/2015; Published online: 16/03/2016



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