Medicinski podmladak

Medical Youth

ORIGINAL ARTICLE

# ASSOCIATION BETWEEN TIME FROM DIAGNOSIS TO INITIATION OF SYSTEMIC THERAPY OF METASTATIC RENAL CELL CARCINOMA WITH TREATMENT OUTCOME

# POVEZANOST DUŽINE VREMENA OD DIJAGNOZE DO POČETKA SISTEMSKE TERAPIJE METASTAZNOG KARCINOMA BUBREŽNIH ĆELIJA SA ISHODOM LEČENJA

Nikola Lisičić[1], Angelina Kević[1], Marko Savić[2], Predrag Nikić[1,3]

[1] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija
[2] Univerzitet u Beogradu, Medicinski fakultet, Institut za medicinsku statistiku i informatiku, Beograd, Srbija
[3] Univerzitetski klinički centar Srbije, Klinika za urologiju, Beograd, Srbija

**Correspondence:** nikola.lisicic1@hotmail.com

## Abstract

**Introduction:** In about 30% of cases, renal cell carcinoma (RCC) is detected initially in the metastatic stage (mRCC). The mainstay of mRCC treatment is anti-angiogenesis targeted therapy and immunotherapy which both have significantly prolonged progression-free survival and overall survival in patients with mRCC.

**Aim:** The aim of this study was to examine the association between the time interval from diagnosis of mRCC to the start of systemic therapy with the radiologically assessed best treatment response after 12 months of therapy.

**Material and methods:** This observational study included 85 patients diagnosed initially in the metastatic stage of RCC. All patients received single-agent systemic targeted therapy sunitinib. The minimum follow-up period was 12 months. The radiologic assessment was performed after every 3 months, and the RECIST criteria were used to evaluate the best treatment response.

**Results:** The mean time interval from mRCC diagnosis to the start of systemic targeted therapy was 3.5 ± 2.5 months, with a median of 2 months. No statistically significant association was observed between the best radiologically assessed treatment response after 12 months of therapy and the time interval from diagnosis of mRCC to the start of systemic targeted therapy ($p = 0.7$). Moreover, no statistically significant association was found between the best radiologically assessed treatment response after 12 months of therapy and a total number of metastatic sites at baseline.

**Conclusion:** No association was observed between the best radiologically assessed treatment response after 12 months of systemic targeted therapy, neither with the time interval from mRCC diagnosis to the start of systemic targeted therapy nor with the total number of metastatic sites in patients who were initially diagnosed with mRCC and received sunitinib in first-line setting.

**Keywords:**
mRCC,
systemic therapy,
treatment response,
observational study,
sunitinib



The authors declare no conflicts of interest.

doi:10.5937/mp74-33350
Editorial board: podmladak.med.bg@gmail.com

## Sažetak

**Uvod:** U oko 30% slučajeva karcinom bubrežnih ćelija (engl. *Renal Cell Carcinoma* - RCC) se otkriva u metastaznom stadijumu (engl. *metastatic RCC* - mRCC). Okosnicu lečenja mRCC predstavljaju antiangiogenezna ciljana terapija i imunoterapija koje su pacijentima sa mRCC značajno produžile preživljavanje bez progresije i ukupno preživljavanje.

**Cilj:** Cilj ovog istraživanja je da se ispita povezanost između vremenskog intervala proteklog od postavljanja dijagnoze mRCC do početka sistemske terapije sa radiografski procenjenim najboljim odgovorom posle 12 meseci terapije.

**Materijal i metode:** Opservaciona studija obuhvatila je 85 pacijenata sa dijagnozom inicijalno metastaznog RCC. U okviru sistemske ciljane terapije svi pacijenti su dobijali lek sunitinib. Minimalni period praćenja iznosio je 12 meseci. Radiografska procena terapijskog odgovora rađena je posle svaka 3 meseca terapije, a za evaluaciju najboljeg terapijskog odgovora korišćeni su RECIST (engl. *Response Evaluation Criteria in Solid Tumors* - RECIST) kriterijumi.

**Rezultati:** Prosečna dužina vremena od trenutka postavljanja dijagnoze mRCC do početka sistemske ciljane terapije je iznosila 3,5 ± 2,5 meseca, sa medijanom od 2 meseca. Nije uočena statistički značajna povezanost između najboljeg radiografski procenjenog terapijskog odgovora posle 12 meseci terapije i vremenskog intervala od postavljanja dijagnoze mRCC do početka sistemske ciljane terapije (p = 0,7). Takođe, nije uočena statistički značajna povezanost između ukupnog broja metastaznih mesta u momentu postavljanja dijagnoze mRCC i najboljeg radiografski procenjenog odgovora posle 12 meseci terapije.

**Zaključak:** Nije uočeno postojanje povezanosti između najboljeg radiografski procenjenog terapijskog odgovora posle 12 meseci primene sistemske ciljane terapije ni sa vremenskim intervalom od postavljanja dijagnoze mRCC do početka sistemske ciljane terapije, ni sa ukupnim brojem metastaznih mesta kod pacijenata sa dijagnozom inicijalno metastaznog RCC.


**Ključne reči:**
mRCC,
sistemska ciljana terapija,
terapijski odgovor,
opservaciona studija,
sunitinib

## Introduction

Renal Cell Carcinoma (RCC) is the 6th leading cancer type in men and the 10th in women. The gender ratio is approximately 2:1 male-to-female. Histologically, the clear cell RCC is the most common type (1, 2).

In about 50% of newly diagnosed cases, the disease is found in the localized, non-metastatic stage (3, 4). At this stage, as being potentially curative, total and partial nephrectomy represent the mainstay of treatment (5, 6). After surgical treatment of a localized disease, local recurrence and/or metastases occur in 20 - 30% of patients, usually within a period of 3 years (7).

However, in about 30% of cases, RCC is primarily detected when the disease is already in the metastatic stage (mRCC) (1, 3). The importance of surgical treatment in this stage is less significant and includes cytoreductive nephrectomy (CN) and/or metastasectomy in certain indications (5, 6). It is resistant to treatment with conventional oncological modalities such as chemotherapy, radiotherapy, and hormone therapy (8). The mainstay of mRCC treatment is VEGF-targeted antiangiogenic therapy and immunotherapy, which have both significantly prolonged progression-free survival and overall survival in patients with mRCC (5, 9). Currently, in Serbia, the only one available is first-line therapy, and patients may receive one of two drugs sunitinib (Sutent) or pazopanib (Votrient), both belonging to the same group of tyrosine kinase inhibitors (5, 10).

The proper time to start systemic targeted therapy is not yet precisely defined. According to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria, initiation of therapy in a period of less than one year from the diagnosis of mRCC is a poor prognostic factor (11). In several studies published to date, in patients with oligometastatic disease, delay in initiating therapy has not been associated with a poorer treatment outcome (6, 12, 13).

Therefore, the aim was to determine the radiologically assessed best treatment response after 12 months of therapy and its relationship with the time interval from diagnosis of mRCC to the start of systemic therapy. In addition, the goal was to examine an association between the total number of metastatic sites and the best radiologically assessed treatment response after 12 months of therapy.

## Material and methods

### Test sample

This observational retrospective study was performed at the Clinic of Urology, University Clinical Center of Serbia. The study group consisted of a total of 85 patients, of whom 68 (80%) were male and 17 (20%) female. All patients were older than 18 years. They all had a histopathologically confirmed diagnosis of clear cell RCC. The diagnosis was made after the CN or the kidney tumor biopsy in the initially metastatic stage of RCC. All patients started treatment in the period from January 1, 2012 to December 31, 2018. Follow-up lasted for a minimum of 12 months, ending on December 31, 2019 or until permanent

discontinuation of therapy for any reason before the end of the follow-up period.

Before initiating systemic targeted therapy, the presence of metastases was radiologically confirmed in all patients, based on the multi-detector row computed tomography (MDCT) of the chest, abdomen and pelvis. Prognostic risk assessment was performed using MSKCC score, and patients were stratified into groups with a good, intermediate and poor prognosis (14) (**table 1**).

**Table 1.** Poor prognosis factors and prognostic groups according to MSKCC (Memorial Sloan-Kettering Cancer Center) prognostic score (14).

| Poor prognosis factors | |
|---|---|
| 1) | Hemoglobin < lower reference value |
| 2) | LDH > 1.5 x upper reference value |
| 3) | Corrected serum calcium > 10mg / dl (2.5mmol / L) |
| 4) | ECOG performance status ≥ 2 |
| 5) | Time from diagnosis to the beginning of systemic therapy < 1 year |
| **Prognostic group** | |
| Good | 0 risk factors present |
| Intermediate | 1 or 2 risk factors |
| Poor | ≥ 3 factors |

LDH – lactate dehydrogenase; ECOG – Eastern Cooperative Oncology Group.

According to administrative rules proposed by the National Health Insurance Fund (NHIF), only patients with a good or intermediate prognosis can receive first-line treatment in Serbia (10).

### Treatment protocol

All patients received sunitinib (Sutent) on a 2/1 dosing schedule (2-weeks-on and 1-week-off). The starting dose was 50 mg once daily and no reduction of dose was observed during the treatment. One cycle of therapy is completed after 6 weeks. After each cycle of therapy, performance status, complete blood count, biochemistry and side effects of therapy were assessed. After every two cycles of therapy, the radiologic assessment was performed following MDCT examination of the chest, abdomen and small pelvis. Response Evaluation Criteria in Solid Tumors (RECIST v.1.1) were used to evaluate treatment response as stable disease, partial response, complete response or disease progression (16). The time from diagnosis of mRCC to the start of systemic therapy is defined as the time that has elapsed from the establishment of a histopathological diagnosis after CN or renal biopsy to the start of systemic targeted therapy. The best treatment response was defined as the best radiologic assessment response recorded according to RECIST criteria after 12 months of therapy in patients who have had at least one MDCT of the chest, abdomen and small pelvis. In patients who discontinued therapy before the first evaluation, it was not possible to radiologically assess the best treatment response. The objective response rate was defined as the sum of complete and partial responses registered after 12 months of therapy.

During the follow-up period of 12 months from the start of therapy, reasons for early treatment discontinuation were disease progression, death due to any reason, a significant side effect of therapy, or other reasons than that previously mentioned (loss of contact, personal request for discontinuation, etc.). Disease progression was defined as radiologic, clinical, or a combination of radiologic and clinical progression.

### Statistical analysis

Continuous data are expressed as mean values with standard deviations or as medians with range where appropriate. Categorical data are presented by absolute numbers with percentages. Spearman rank correlation coefficient was used to test the association between ordinal and continuous variables. Statistical significance was tested at the level of 0.05, while the SPSS statistical software (SPSS for Windows, release 21.0, SPSLS, Chicago, I) was used for statistical analysis.

## Results

Out of a total number of 85 patients included in the study, 68 were male (80%) and 17 (20%) female. The mean age of the patients at the time of mRCC diagnosis was 59.2 ± 10.3 years.

According to MSKCC prognostic criteria, all patients had an intermediate prognosis. Time less than 12 months from diagnosis of mRCC to systemic treatment was found in 84 (98.83%) patients.

In a majority of patients, the ones initially diagnosed with metastatic disease have undergone CN prior to systemic therapy (80, 94.1%). According to the number of metastatic sites, 18 patients (21%) had one, 31 patients (37%) had two, and 36 patients (42%) had three or more sites with metastases. No statistically significant association was observed between the total number of metastases and the best radiologically assessed response to therapy after 12 months ($p = 0.090$). The demographic and clinical characteristics of patients with mRCC at the treatment baseline are presented in **table 2**.

The mean time interval from mRCC diagnosis to the start of systemic targeted therapy was 3.5 ± 2.5 months, with a median of 2 months. In majority, treatment started 1 to 3 months after histopathologically confirmed diagnosis of mRCC (**figure 1**).

After 12 months of treatment, 68 patients (80%) were evaluable for the best treatment response. Complete response was registered in one (2%), partial response in 9 (13%), and stable disease in 58 (85%) patients. Objective response was registered in 10 patients and the objective response rate was 15%. Treatment response was not evaluated in 17 patients (20%) since they discontinued therapy before the first evaluation. No statistically significant association was observed between the best radiologically assessed treatment response after 12 months

**Table 2.** Demographic and clinical characteristics of patients with mRCC before starting systemic therapy.

| Characteristic | n (%) |
|---|---|
| Number of patients | 85 (100) |
| Gender | |
| Male | 68 (80) |
| Female | 17 (20) |
| Age at the time of mRCC diagnosis | |
| Mean ± SD | 59.2 ± 10.3 |
| Median (min-max) | 61 (35 – 81) |
| CN before starting therapy | |
| Yes | 80 (94) |
| No | 5 (6) |
| Number of metastases at the beginning of therapy | |
| 1 | 18 (21) |
| 2 | 31 (37) |
| ≥ 3 | 36 (42) |

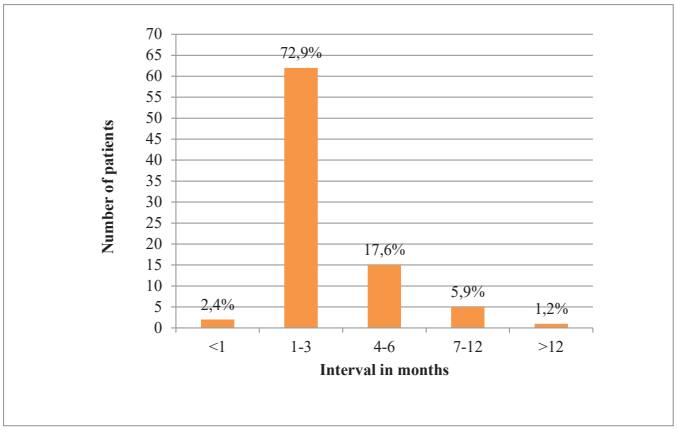


**Figure 1.** Distribution of patients according to the time interval from the diagnosis of mRCC to the beginning of systemic targeted therapy.

of therapy and the time interval from mRCC diagnosis to the start of systemic targeted therapy (p = 0.744). Data related to the assessment of the best treatment response after 12 months of therapy are shown in **table 3**.

**Table 3.** Evaluation of the best treatment response after 12 months of therapy.

| Characteristic | n (%) |
|---|---|
| Radiologically assessed best treatment response after 12 months of therapy | 68/85 (80) |
| Complete response (CR) | 1 (2) |
| Partial response (PR) | 9 (13) |
| Objective response rate (CR + PR) | 10 (15) |
| Stable disease (SD) | 58 (85) |
| Not evaluated | 17/85 (20) |

After the 12-month follow-up, 56 patients (66%) continued with therapy, while 29 patients (34%) were permanently discontinued. Reasons for permanent discontinuation of the first-line treatment were disease progression in 10 patients (34%) and death in 13 patients (45%). There was no permanent discontinuation of treatment due to side effects of therapy, and 6 patients (21%) permanently stopped with treatment due to reasons other than mentioned above (**table 4**).

**Table 4.** Reasons for treatment discontinuation.

| Reason for discontinuation | n (%) |
|---|---|
| Disease progression | 10 (34) |
| Death | 13 (45) |
| Side effects of therapy | 0 (0) |
| Other | 6 (21) |

## Discussion

In patients diagnosed with mRCC, the proper time to start systemic targeted therapy is not well defined. According to MSKCC prognostic criteria, initiation of therapy in a period of less than one year from the diagnosis of mRCC is one of the factors of poor prognosis (11). In this study, the association between the time from diagnosis of mRCC to the start of systemic targeted therapy with radiologically assessed best treatment response after 12 months of therapy was examined. The mean time interval from the time of mRCC diagnosis to the start of systemic targeted therapy in the study was 3.5 ± 2.5, and the median was 2 months, which was not significantly different from the results reported so far in the literature (mean length 3.3, and median 1 month) (17). The results did not show a statistically significant correlation between radiologically assessed best treatment response and time interval from diagnosis of mRCC to initiation of targeted therapy (rs = -0.036; p = 0.744). Currently, there are still no validated diagnostic tests that can accurately predict the treatment response to systemic targeted therapy in patients with mRCC. This is important to note, given that according to the MSKCC prognostic score, one of the factors of poor prognosis is the initiation of systemic therapy in the first 12 months from the time of mRCC diagnosis (11). Therefore, the majority of patients initially diagnosed with mRCC will inevitably have an MSKCC median prognosis due to the existence of this risk factor in the overall score.

To the best of our knowledge, there are no published data with regard to the relationship between the time from diagnosis of mRCC to the start of systemic targeted therapy with radiologically assessed best treatment response after 12 months of therapy. Moreover, there are no published studies investigating only the population of patients initially diagnosed with mRCC. Therefore, a direct comparison of the results with data from the literature is not possible. However, according to the results of one retrospective study, it has been shown that patients who start

therapy within the first 100 days from the time of diagnosis have a statistically significant faster progression of the disease (18). In this study, 27% of patients permanently discontinued therapy due to disease progression or death for any reason within 12 months of initiating targeted therapy.

The next segment of the study was to investigate the association between the total number of metastatic sites and the best radiologically assessed treatment response after 12 months of therapy in patients initially diagnosed with mRCC. The distribution of patients according to the number of metastatic sites was consistent with the results of other researchers (19). The analysis of data obtained in this study did not show a statistically significant correlation between the total number of metastatic sites and the best response to therapy after 12 months ($p = 0.090$). Based on the available published data, so far no study has examined the association between the total number of metastatic sites and the best response to therapy after 12 months. The number and location of metastases are not included as factors of poor prognosis in mRCC patients receiving systemic targeted therapy, in none of the validated prognostic scores, MSKCC and IMDC (International Metastatic RCC Database Consortium) (5, 6).

## Conclusion

No association was observed between the best radiologically assessed treatment response after 12 months of therapy, either with the time interval from diagnosis of mRCC to the start of the systemic targeted therapy, or with the total number of metastatic sites. Delayed initiation of systemic targeted therapy in patients initially diagnosed with mRCC was not associated with poorer radiologically assessed best treatment response after 12 months of therapy.

## Literature


1. Padala SA, Barsouk A, Thandra KC, Saginala K, Mohammed A, Vakiti A, et al. Epidemiology of Renal Cell Carcinoma. World J Oncol. 2020; 11(3):79-87.
2. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, et al. Epidemiology of Renal Cell Carcinoma. Eur Urol. 2019; 75(1):74-84.
3. Cairns P. Renal cell carcinoma. Cancer Biomark. 2010; 9(1-6):461-73.
4. Gray RE, Harris GT. Renal Cell Carcinoma: Diagnosis and Management [published correction appears in Am Fam Physician. 2019 Jun 15; 99(12):732]. Am Fam Physician. 2019; 99(3):179-84.
5. EAU Guidelines: Renal Cell Carcinoma | Uroweb. [Accessed 3rd January 2021], Available from: https://uroweb.org/guideline/renal-cell-carcinoma/.
6. Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019; 30(5):706-20.
7. Sato T, Kawasaki Y, Maekawa M, Takasaki S, Saigusa D, Ota H,et al. Value of global metabolomics in association with diagnosis and clinicopathological factors of renal cell carcinoma. Int J Cancer. 2019; 145(2):484-93.
8. Yuan ZX, Mo J, Zhao G, Shu G, Fu HL, Zhao W. Targeting Strategies for Renal Cell Carcinoma: From Renal Cancer Cells to Renal Cancer Stem Cells. Front Pharmacol. 2016; 7:423.
9. Molina AM, Motzer RJ. Clinical practice guidelines for the treatment of metastatic renal cell carcinoma: today and tomorrow. Oncologist. 2011; 16:45-50.
10. Lista C. Lekovi sa posebnim režimom izdavanja. [Accessed 4th January 2021], Available from: https://www.rfzo.rs/download/pravilnici/lekovi/C%Lista_primena%od%04.04.2020..pdf.
11. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009; 27(34):5794-9.
12. Fisher R, Pender A, Thillai K, Chowdhury S, Pickering L, Khabra K, et al. Observation as a treatment strategy for advanced renal cell carcinoma-a call for prospective validation. Front Oncol. 2012; 2:155.
13. Rini BI, Dorff TB, Elson P, Rodriguez CS, Shepard D, Wood L, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol. 2016; 17(9):1317-24.
14. Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 2013; 14(2):141-8.
15. Neeman E, Gresham G, Ovasapians N, Hendifar A, Tuli R, Figlin R, et al. Comparing Physician and Nurse Eastern Cooperative Oncology Group Performance Status (ECOG-PS) Ratings as Predictors of Clinical Outcomes in Patients with Cancer. Oncologist. 2019; 24(12):e1460-e1466.
16. Morgan RL, Camidge DR. Reviewing RECIST in the Era of Prolonged and Targeted Therapy. J Thorac Oncol. 2018; 13(2):154-64.
17. Maroun R, Mitrofan L, Benjamin L, Nachbaur G, Maunoury F, Le Jeunne P, et al. Real life patterns of care and progression free survival in metastatic renal cell carcinoma patients: retrospective analysis of cross-sectional data. BMC Cancer. 2018; 18(1):214.
18. Badran A, Elshenawy MA, Shahin A, Aljubran A, Alzahrani A, Eldali A, et al. Efficacy and Prognostic Factors of Sunitinib as First-Line Therapy for Patients With Metastatic Renal Cell Carcinoma in an Arab Population. JCO Glob Oncol. 2020; 6:19-26.
19. van der Veldt AA, Boven E, Helgason HH, van Wouwe M, Berkhof J, de Gast G, et al. Predictive factors for severe toxicity of sunitinib in unselected patients with advanced renal cell cancer. Br J Cancer. 2008; 99(2):259-65.