ORIGINAL ARTICLE

Prognostic factors influencing survival rates in elderly patients with metastatic renal cell carcinoma

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ABSTRACT

Purpose of the study. To determine the influence of prognostic factors on survival rates in patients with mRCC aged ≥ 75 years.
Materials and methods. A retrospective study included 77 mRCC patients aged ≥ 75 years who received systemic therapy at the Municipal Oncologic Hospital No. 62 in Moscow and the Municipal Oncologic Dispensary in St. Petersburg from 2006 to 2019. Clinical data from medical records were obtained and analyzed retrospectively, all patients underwent clinical, laboratory, and pathomorphological examination. Patients' survival rates were evaluated using the statistical method of survival time analysis (Survival Analysis). Descriptive characteristics of survival time were calculated in the form of life tables, and Kaplan-Meier curves were constructed.
Results. In the present study, a favorable prognosis according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)was noted in 20.8 % of patients with mRCC aged ≥ 75 years; 6.5 % had solitary metastases. The 3- and 5-year survival rates were 35.8 % and 21.2 %.
In single-factor analysis in mRCC patients ≥ 75 years of age, it was found that ECOG status ($p < 0.001$), histological subtype ($p = 0,01$), Fuhrman grade of tumour differentiation ($p = 0.003$), type of metastases ($p = 0.045$), liver metastases ($p < 0.001$), IMDC prognosis ($p = 0.042$) and nephrectomy ($p = 0.014$).
Conclusion. In a multivariate analysis, factors affecting survival in patients with mRCC aged ≥ 75 years included sex, histologic subtype, number of metastases, bone and lymph node metastases, IMDC prognosis, and radiation therapy and nephrectomy. Further studies are needed to identify additional personalized prognostic factors in elderly patients with metastatic renal cell carcinoma (mRCC).

Keywords: metastatic renal cell carcinoma, overall survival rate, elderly patients

ОРИГИНАЛЬНАЯ СТАТЬЯ

Прогностические факторы, влияющие на показатели выживаемости у больных старческого возраста с метастатическим почечноклеточным раком

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РЕЗЮМЕ

Цель исследования. Определить влияние прогностических факторов на показатели выживаемости у пациентов с метастатическим почечно-клеточным раком (мПКР) в возрасте ≥ 75 лет.

Материалы и методы. В ретроспективное исследование были включены 77 пациентов с мПКР в возрасте ≥ 75 лет, которые получали системную терапию на базе Городской онкологической больнице № 62 г. Москвы и Городском онкологическом диспансере г. Санкт-Петербурга с 2006 по 2019 гг. Клинические данные из медицинских карт были получены и проанализированы ретроспективно, всем пациентам было проведено клинико-лабораторное, патоморфологическое исследование. Показатели выживаемости пациентов оценивали с помощью статистического метода анализа времени жизни (Survival Analysis) с расчетом описательных характеристик времени жизни в форме таблицы жизни и построения кривых Каплана-Мейера.

Результаты. В настоящем исследовании благоприятный прогноз по IMDC у больных с мПКР ≥ 75 лет отмечен у 20,8 % пациентов, солитарные метастазы у 6,5 %. Показатели 3 и 5-тилетней выживаемости составили 35,8 % и 21,2 %.

При однофакторном анализе у больных мПКР ≥ 75 лет, выявлено, что отрицательное влияние на показатели выживаемости оказывали ECOG статус ($p < 0,001$), гистологический подтип ($p = 0,01$), степень дифференцировки опухоли по Fuhrman ($p = 0,003$), тип метастазов ($p = 0,045$), метастазы в печень ($p < 0,001$), прогноз по IMDC ($p = 0,042$) и проведение нефрэктомии ($p = 0,014$).

Заключение. Факторами, влияющими на показатели выживаемости у пациентов с мПКР в возрасте ≥ 75 лет, при многофакторном анализе являлись пол, гистологический подтип, количество метастазов, метастазы в кости и лимфатические узлы, прогноз по IMDC, а также проведение лучевой терапии и нефрэктомии.

Для определения дополнительных персонализированных факторов прогноза у больных старческого возраста с мПКР необходимы дальнейшие исследования.

Ключевые слова: метастатический почечно-клеточный рак, общая выживаемость, пожилые пациенты

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Семенов Д. В.✉, Орлова Р. В., Широкорад В. И., Кострицкий С. В., Кононец П. В. Прогностические факторы, влияющие на показатели выживаемости у больных
старческого возраста с метастатическим почечноклеточным раком

INRODUCTION

Over the past decade, the incidence of RCC has been increasing annually. RCC occurs in 25 % of patients with newly diagnosed RCC over the age of 75 ([1]. Currently, the majority of patients with metastatic renal cell carcinoma (mRCC) receive various options for systemic therapy, due to which the median overall survival (s) increased to 4 years [2, 3]. It is known that in elderly patients, the activity of the tumor process is lower due to a slowdown in metabolic processes in the body. The implementation of modern drug therapy contributes to an increase in the indicators of OS in patients with mRCC, including in elderly patients [4]. But aggressive systemic therapy in patients over 75 years of age is associated with an increased risk of undesirable side effects that worsen the quality of life. In our study, we studied prognostic factors in patients with mRCC aged ≥ 75 years, affecting survival rates.

MATERIALS AND METHODS

A retrospective analysis of 77 patients aged ≥ 75 years who received systemic therapy at the Moscow City Oncological Hospital No. 62 and

Table 1. Characteristics of patients	
Characteristic	≥ 75 лет (n = 77) n (%)
Gender: male female	 51 (66.2) 26 (33.8)
ECOG status: 0 1 2 3	 1 (1.3) 29 (37.7) 35 (45.5) 12 (15.6)
Histological type: clear-cell carcinoma non-clear-carcinoma	 64 (83.1) 13 (16.9)
Differentiation grade: G1 G2 G3	 18 (23.4) 27 (35.1) 32 (41.6)
Metastasis type: metachronous synchronous	 53 (68.8) 24 (31.2)
Number of metastases: solitary single multiple	 5 (6.5) 27 (35.1) 45 (58.4)
IMDC prognosis: favorable intermediate poor	 16 (20.8) 32 (41.6) 29 (37.7)
Metastatic site: lungs bones liver lymph nodes	 48 (62.3) 26 (33.8) 6 (7.8) 21 (27.3)
Prior nephrectomy:	71 (92.2)
Metastasectomy:	11 (14.3)
Radiation therapy:	10 (13)

the St. Petersburg City Oncological Dispensary from 2006 to 2019 was carried out. All patients received systemic antitumor therapy. The influence of clinical and morphological factors on overall survival(s) was assessed. Detailed characteristics of patients are given in Table 1.
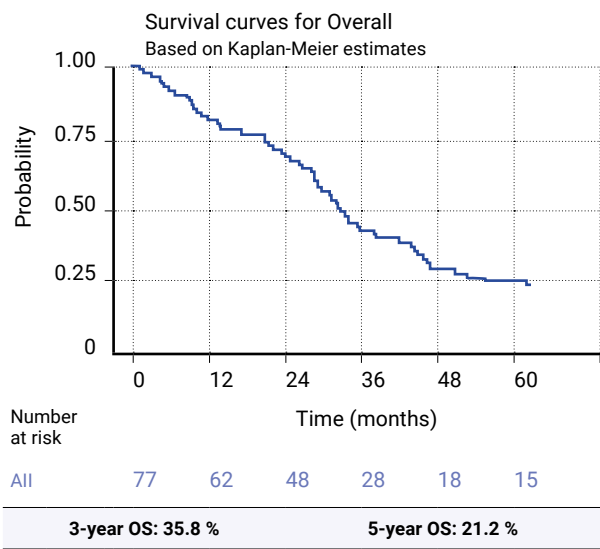
Fig. 1. Overall survival (OS) of patients ≥ 75 years of mRCC (n = 77)

Patient data was consolidated in the form of spreadsheets and analyzed using the Statistica 12 for Windows program. Life expectancy was calculated from the date of diagnosis to the date of last observation or death. Survival was assessed using the Kaplan-Mayer method, survival differences were determined using a log-rank test; Cox regression analysis was used to exclude factors that do not have independent prognostic significance. An analysis of the S of patients with mRCC ≥ 75 years old was performed, depending on the histological variant of the tumor, the degree of tumor differentiation according to Fuhrman, the IMDC prognosis group, the number, type and localization of metastases, cytoreductive surgery and radiation therapy.

STUDY RESULTS

The clinical and morphological characteristics of 77 patients are presented in Table 1. The average age was 79 (75–95) years. Clear cell renal cell carcinoma was detected in 64 (83.1 %) patients. Favorable, intermediate and unfavorable forecast for IMDC in 16 (20,8 %), 32 (41,6 %) and 29 (37.7 %) patients. Solitary, single and multiple metastases

Fig. 2. Overall survival (OS) in patients ≥ 75 years of mRCC depending on histologic subtype (A) and tumor differentiation according to Fuhrman (B) (n = 77)

were detected in 5 (6,5 %), 27 (35,1 %) and 45 (58.4 %) patients, respectively.

The indicators of 3- and 5-year OV in patients with mRCC were 39.7 % [29.8–52.76 %; 95 % CI] and 21.2 % [13.6–33.24 %; 95 % CI], respectively,

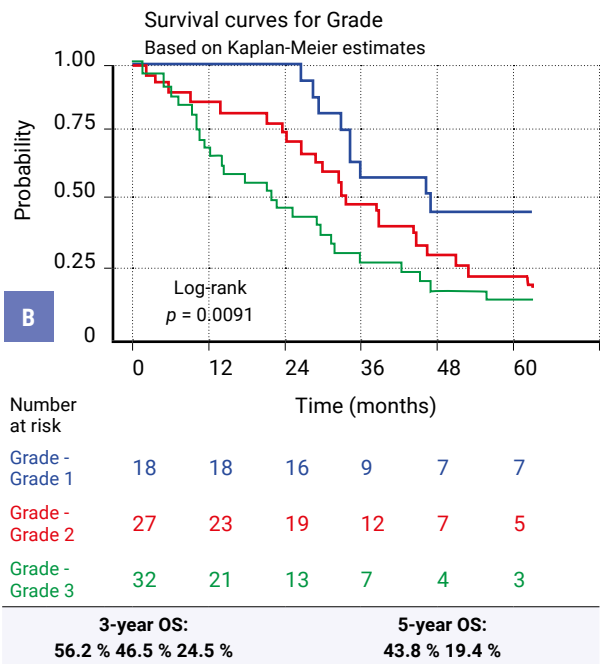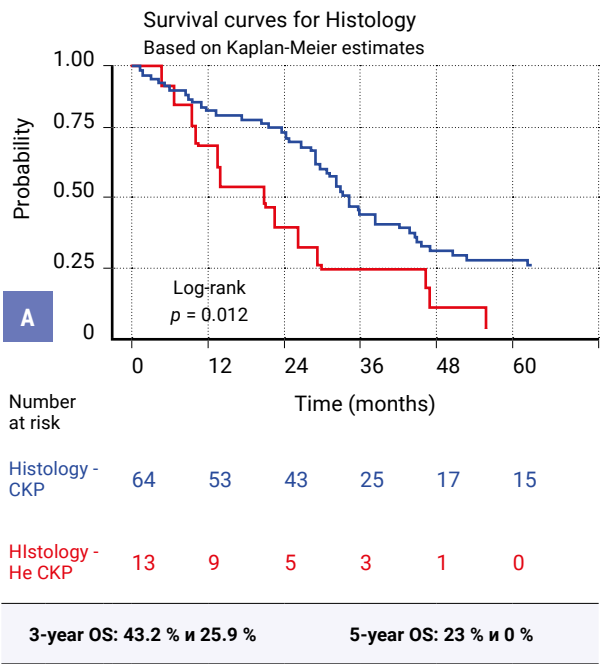in patients, while the median OS was 32.4 [28.9–38.6 %; 5 % CI] months (Fig. 1).

A single-factor analysis in patients with mRCC ≥ 75 years old revealed that ECOG status ($p < 0.001$), histological subtype ($p = 0.01$), degree

Survival curves for Type
Based on Kaplan-Meier estimates

Log-rank
$p = 0.043$

Number at risk	0	12	24	36	48	60
Type = Synchronous MTC (2)	24	16	11	7	2	2
Type = Metachronous MTC	53	46	37	21	16	13

3-year OS: 43.6 % and 30.7 %	5-year OS: 27.0 % and 8.8 %

Survival curves for Hepar
Based on Kaplan-Meier estimates

Log-rank
$p < 0.0001$

Number at risk	0	12	24	36	48	60
Hepar - Liver metastases (-)	71	60	47	28	18	15
Hepar - Liver metastases (+)	6	2	1	0	0	0

3-year OS: 43.1 %	5-year OS: 223.1 %	1-year OS: 33.3%

Fig. 3. Overall survival (OS) in patients ≥ 75 years of mRCC according to type of metastases (A) and liver metastases (B) (*n* = 77)

Survival curves for IMDC
Based on Kaplan-Meier estimates

Log-rank
$p = 0.00032$

Number at risk	0	12	24	36	48	60
IMDC - Favorable	16	15	13	9	7	7
MOC - Intermediate	32	27	23	14	7	6
IMDC - Unfavorable	29	20	12	5	4	2

3-year OS: 64.9 % 47.2 % 18.0 %	5-year OS: 50.5 % 20.2 % 7.2 %

Survival curves for CN
Based on Kaplan-Meier estimates

Log-rank
$p = 0.0096$

Number at risk	0	12	24	36	48	60
CN - ЦНЭ (+)	71	59	46	27	18	15
CN - ЦН3 (-)	6	3	2	1	0	0

3-year OS: 41.6 % 16.7 %	5-year OS: 23.1 % 0 %

Fig. 4. Overall survival (OS) in patients ≥ 75 years depending on prognosis IMDC (A) and nephrectomy performance (B) (*n* = 77)

Table 2. Prognostic factors for overall survival in patients ≥ 75 years of age with mRCC (*n* = 77) (single-factor and multivariate analysis)*

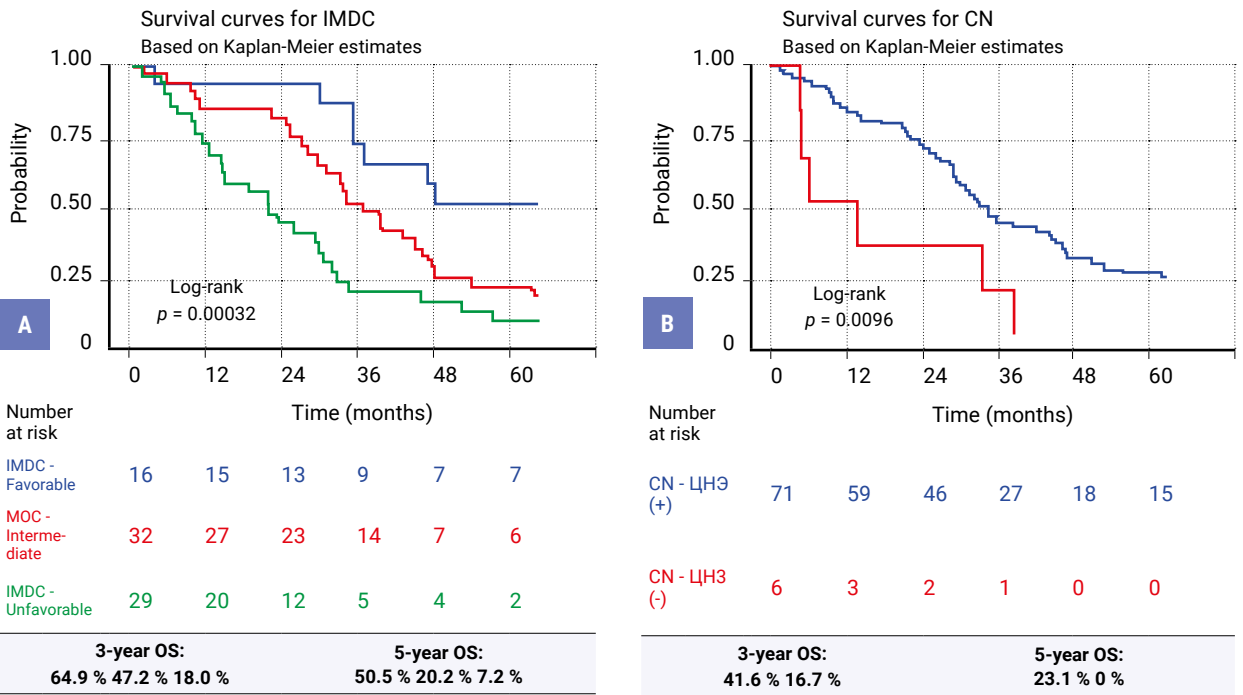| Factor	Hazard rario (95 % confidence interval)	
	Univariate test	Multivariate test
Gender: male female	– 0.62 (0.37−1.05, *p* = 0.077)	– 0.27 (0.16−0.46, *p* < 0.001)
ECOG status: 0 1 2 3	– 20379783.9 (0.00-Inf, *p* = 0.997) 38320352.5 (0.00-Inf, *p* = 0.997) 82331370.5 (0.00-Inf, *p* = 0.996)	– 41895.8 (24218−1572477.23, *p* < 0.001) 69920.5 (41671.28−117320.25, *p* < 0.001) 112174.0(53540.28-235019.58, *p* < 0.001)
Histological type: clear-cell carcinoma non-clear-carcinoma	– 2.19 (1.17−4.09, *p* = 0.014)	– 1.92 (1.02−3.60, *p* = 0.043)
Differentiation grade: G1 G2 G3	– 1.74 (0.90−3.36, *p* = 0.100) 2.71 (1.40−5.25, *p* = 0.003)	– 1.43 (0.86−2.36, *p* = 0.169) 1.38 (0.83−2.32, *p* = 0.218)
Metastasis type: metachronous synchronous	– 0.59 (0.35−0.99, *p* = 0.045)	– 1.22 (0.71−2.08, *p* = 0.478)
Number of metastases: solitary single multiple	– 0.64 (0.24−1.71, *p* = 0.372) 1.33 (0.52−3.42, *p* = 0.553)	– 0.59 (0.35−1.00, *p* = 0.050) 1.66 (1.00−2.73, *p* = 0.049)
Lung metastases: present absent	– 1.58 (0.38-6.64, *p* = 0.532)	– 1.29 (0.81−2.08, *p* = 0.139)
Bone metastases: present absent	1.17 (0.69−1.98, *p* = 0.557)	3.09 (1.82−5.23, *p* < 0.001)
Liver metastases: present absent	– 6.68 (2.74−16.28, *p* < 0.001)	– 1.86 (0.74−4.69, *p* = 0.186)
Lymph nodes metastases: present absent	– 1.16 (0.68−1.97, *p* = 0.595)	– 0.54 (0.31−0.93, *p* = 0.026)
IMDC prognosis: favorable intermediate poor	– 4.00 (1.93-8.29, *p* < 0.001) 2.07 (1.03−4.18, *p* = 0.042)	– 1.94 (1.13−3.33, *p* = 0.016) 1.93 (1.17−3.20, *p* = 0.010)
Radiation therapy: no yes	– 0.99 (0.44-2.20, *p* = 0.979)	– 0.28 (0.12-0.64, *p* = 0.002)
Prior nephrectomy: yes no	– 2.95 (1.25-6.99, *p* = 0.014)	– 6.08 (2.54−14.58, *p* < 0.001)
Metastasectomy	0.41 (0.05−3.53, *p* = 0.419)	0.65 (0.28−1.46, *p* = 0.323)

Note: the table only presents factors with prognostic significance

of tumor differentiation according to Fuhrman ($p = 0.003$), type of metastases ($p = 0.045$), liver metastases had a negative effect on survival rates ($p < 0.001$), IMDC prognosis ($p = 0.042$) and nephrectomy ($p = 0.014$) (Table 2, Fig. 2–4).

The median OS in clear cell and non-light cell cancers was 34.4 [30.0–44.6; 95 % CI] and 21.2 [10.4–NA; 95 % CI] months, respectively, and in G1, G2 and G3 was 46.4 [34.4–NA; 95 % CI], 33,4 [26,9–51; 95 % CI] and 21.7 [13.9–31.6; 95 % CI] months, respectively.

The median S in metachronous and synchronous metastases was 33 [29.1–46.9; 95 % CI] and 23.7 [12–44.6; 95 % CI] months, respectively, and in the absence and presence of liver metastases was 33.4 [29.1–44.6; 95 % CI] and 5.1 [3.5–NA; 95 % CI] months, respectively.

The median OS with favorable, intermediate and unfavorable forecasts was 65.2 [35.9–NA; 95 % CI], 35,8 [29–46,3; 95 % CI] and 21.2 [13.7–31.1; 95 % CI] months, respectively, and in the presence or absence of nephrectomy was 32.6 [29–44.6; 95 % CI] and 10 [5–NA; 95 % CI] months, respectively.

In multivariate analysis, gender [HR = 0.27 (95 % CI = 0.16–0.46], ECOG status [HR = 112174.0 (95 % CI = 53540.28–235019.58], histological subtype [HR = 1.92 (95 % CI = 1.02–3.60], number of metastases [HR = 1.66 (95 % CI = 1.00–2.73], bone metastases [HR = 3.09 (95 % CI = 1.82–5.23] and lymph nodes [HR = 0.54 (95 % CI = 0.31–0.93], IMDC prognosis [HR = 1.93 (95 % CI = 1.17–3.20], as well as radiation therapy [HR = 0.28 (95 % CI = 0.12–0.64] and nephrectomy [HR = 6.08 (95 % CI = 2.54–14.58] were additional factors that had an independent negative effect on the indicators of OS in elderly patients with mRCC (Table 2).

DISCUSSION

Currently, due to an increase in life expectancy, the number of senile patients with renal cell carcinoma is growing in the world, 25 % of patients over 75 years of age are diagnosed with RCC for the first time ([1]. In a retrospective study by Kanesvaran R et al. old age does not affect the indicators of OS in mRCC [5]. In our study, the rates of 3-

and 5-year-olds in patients with mRCC ≥ 75 years were 35.8 % and 21.2 %. In the work of Ryuichi Mizuno et al. A decrease in OS in senile patients is possible due to an unbalanced distribution of patients in the IMDC prognosis groups, a higher incidence of anemia, as well as a higher percentage of patients receiving symptomatic therapy instead of second-line systemic therapy [6]. In our study, anemia was noted in 35.1 % of patients, 1/5 of patients in the group with a favorable prognosis according to IMDC, one third of patients had bone metastases.

The decrease in OS indicators may occur due to ineffective therapy of senile patients and early transfer of this category to symptomatic treatment [7]. Modern drug therapy over the past few decades has led to a significant increase in OS rates in patients with mRCC. Elderly patients after the first line of systemic therapy are not always transferred to the second line due to the high risk of adverse events. This is due to a lack of evidence that elderly patients can tolerate systemic therapy of two or more lines in order to increase the indicators of OS. Currently, in addition to prognostic prognostic factors, personalized therapeutic strategies are being developed [8, 9]. In our study, we identified additional prognostic factors affecting survival rates in senile patients with mRCC.

The limitations of this study are the size of the studied group of patients and its retrospective nature. Further research is needed to develop personalized approaches in elderly patients with mRCC to improve the quality of life and increase the indicators of OS.

CONCLUSION

The factors influencing survival rates in patients with mRCC aged ≥ 75 years in multivariate analysis were gender, histological subtype, number of metastases, bone and lymph node metastases, IMDC prognosis, as well as radiation therapy and nephrectomy.

Further studies are needed to determine additional personalized prognostic factors in senile patients with mRCC.

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Contribution of the authors:

Semenov D. V. – collection of material, analysis of the obtained data, writing the manuscript;
Orlova R. V. – analysis of the obtained data, editing of the manuscript;
Shirokorad V. I. – development of the study design, obtaining data for analysis, editing of the manuscript;
Kostritsky S. V. – collection of material, analysis of the obtained data.