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PROGNOSTIC VALUE OF TUMOR GROWTH RATE AND BIOMARKER DYNAMICS IN PATIENTS WITH RENAL CELL CARCINOMA

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The article discusses the features of the main modern prognostic models in patients with metastatic renal cell carcinoma. The possibilities of using molecular biological markers associated with the activation or proliferation of tumor cells and the microenvironment are highlighted. The possibility of integrating parameters that reflect the intensity of growth or decrease in the volume of tumor mass into prognostic systems is shown. Data from our own research is presented. A model is presented that, along with the components used earlier, includes immunological parameters (spontaneous production of IL-6 and IL-8) and kinetic parameters of tumor growth or regression. These factors are associated with the degree of malignancy and aggressiveness, and are independent predictors. The article presents literature data on the relationship of the studied components of the immune system with invasiveness, proliferative activity and metastatic potential of the tumor. Future research directions are outlined regarding the possibility of integrating biomarkers into predictive models for renal cell carcinoma.

Keywords: renal cell carcinoma; prognostic models; immunotherapy; volumetry; biomarkers; tumor growth rate; interleukin-6; interleukin-10; proinflammatory cytokines; acute phase proteins.

ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ СКОРОСТИ РОСТА ОПУХОЛИ И ДИНАМИКИ БИОМАРКЕРОВ У БОЛЬНЫХ ПОЧЕЧНО-КЛЕТОЧНЫМ РАКОМ

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В статье рассмотрены особенности основных современных моделей прогнозирования у больных метастатическим почечно-клеточным раком. Изучены возможности использования молекулярно-биологических маркеров, связанных с активацией или пролиферацией клеток опухоли и микроокружения. Показана возможность интеграции параметров, отражающих интенсивность роста или уменьшения объема опухолевой массы в прогностические системы. Приведены данные собственных исследований. Представлена модель, которая наряду с компонентами, использованными ранее, включает иммунологические показатели (спонтанная продукция IL-6 и IL-8) и кинетические параметры роста или регресса опухоли. Эти факторы связаны со степенью злокачественности и агрессивностью и являются независимыми предикторами. В кратком обзоре отражена взаимосвязь исследованных компонентов иммунной системы с инвазивностью, пролиферативной активностью и метастатическим потенциалом опухоли. Намечены направления будущих исследований, касающиеся возможности интеграции биомаркеров в прогностические модели для почечно-клеточного рака.

Ключевые слова: почечно-клеточный рак; прогностические модели; иммунотерапия; волюметрия; биомаркеры; скорость роста опухоли; интерлейкин-6; интерлейкин-10; провоспалительные цитокины; белки острой фазы.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2%–4% of all adult tumors. Approximately 300,000 new cases are diagnosed worldwide each year, and more than 100,000 patients die from RCC. In the United States, 73,820 new RCC cases were detected in 2019, and 14,770 people died. In the Russian Federation, the incidence rate is growing steadily. Thus, from 2011

to 2019, the prevalence increased from 78.5 to 128.2 per 100,000 population. The histological structure of 70%–85% of tumors is clear cell carcinoma. The average age of initial detection is 64 years. In 30% of patients, distant metastases are detected at the initial visit. They develop in another 30% within one year after radical surgery. Metastases cause death in 40% of cases. In the general population of RCC patients, the five-year survival rate with locally advanced forms is 67% and 12% in the presence of distant metastases. In specialized centers, where all the available options for surgical and drug treatment can be used, and the intervals for instrumental assessment of effectiveness are maintained very clearly, this indicator reaches 23% [1, 2].

The study of prognostic factors and the creation of models for RCC are associated with both the emergence of new effective treatment methods and the clarification of the role of several molecular biological factors in carcinogenesis. Clinical, anatomical, histological, immunohistochemical, humoral, and immunological factors are used in the models developed.

When creating prognostic scales, three stages are traced, associated with the improvement of diagnostics and new methods for treating RCC. At stage 1, prognostic systems were created based on clinical data, and at stage 2, biochemical parameters were included. Stage 3 is characterized by the use of components that reflect the degree of the tumor's aggressiveness. Diagnostic systems can be represented by predictive scales or mathematical models. Based on the prediction object, they can be divided into those used for local and locally advanced forms of RCC and developed for disseminated forms.

Currently, the MSKCC (Memorial Sloan-Kettering Cancer Center) scale, the French immunotherapy group scale, the Cleveland clinic scale, the model of the international working group for the study of kidney cancer, the model of the International Metastatic RCC Database Consortium, and a model created when studying the efficacy and safety of Sunitinib in phase 3 clinical trials, and widely used for metastatic RCC [3]. They differ in the set of parameters used and the endpoints for evaluating treatment effectiveness (Table 1).

Table 1 / Таблица 1

Predictive models of metastatic renal cell carcinoma
Прогностические модели метастатического почечно-клеточного рака

Parameters	MSKCC [4]	French Immunotherapy Group [5]	International Renal Cancer Group [6]	Cleveland Clinic [7]	IMDC [8]	Sunitinib, phase III [9]
Endpoints	OSR	OSR	OSR	PFS	OSR	OSR
Karnofsky index	+	+	+	+	+	+
Period to treatment start	+	–	+	+	+	+
Number of metastases	–	+	+	–	–	–
Bone metastases	–	–	–	–	–	+
Time to progression	–	+	–	–	–	–
Signs of inflammation	–	+	–	–	–	–
Immunotherapy	–	–	+	–	–	–
Alkaline phosphatase	–	–	+	–	–	–
Calcium	+	–	+	+	+	+
LDH	+	–	+	–	–	+
Hemoglobin	+	+	+	–	+	+
Neutrophils	–	–	–	+	+	–
Leukocytes	–	–	+	–	–	–
Platelets	–	–	–	+	+	–

Note. MSKCC – Memorial Sloan-Kettering Cancer Center; IMDC – International Metastatic Renal Cancer Database Consortium; OSR – overall survival rate; PFS – progression-free survival; LDH – lactate dehydrogenase.

Over the past 10 years, researchers have been trying to integrate molecular biological parameters, and tumor growth rate indicators into previously developed prognostic scales. The emphasis is made on genetic research and the study of RCC molecular subtypes. However, there are several problems associated with the technical difficulties in introducing modern technologies into clinical practice. For instance, they are associated with the complexity of interpreting studies that use biomarkers. At present, recommendations for the standardization of biomarker studies have been developed and are being implemented [10–12].

MATERIALS AND METHODS

For prognostic model development, the study used data of 92 patients who were monitored at the A.M. Granov Russian Research Center of Radiology and Surgical Technologies of the Ministry of Health of the Russian Federation from 2011 to 2020. These included 52 (57%) women and 40 (43%) men, with the female/male ratio of 1.3. The patients enrolled in the study were 61 ± 7.5 years (41 to 82 years). Most patients (72 patients, 78.3%) belonged to 50 to 69 years old.

The model was validated using a group of patients monitored from 1998 to 2010. Data on the study of the efficiency of various chemoimmunotherapy regimens and the studied prognostic factors in this group were published earlier [13–20]. A total of 261 people participated in the study. They included 172 (66%) women and 89 (34%) men, with a female/male ratio of 1.9. The patients' ages included in the study were 57 ± 9.5 years (35 to 84 years). Most of them (182 patients, 69.7%) also belonged to the age category of 50 to 69 years old. The clinical characteristics of the study group and the validation group are presented in Table 2.

Before the treatment onset, the patients underwent a computed tomography study on a Somatom-CR apparatus according to the standard technique with 2 to 5 mm increments, with contrast enhancement (Omnipaque and Ultravist). If computed tomography was impossible, magnetic resonance imaging was performed using a Magneton Vision apparatus to determine the lesion's extent in the abdominal cavity, small pelvis, bones, brain, and spinal cord. Computed tomography and magnetic resonance imaging were performed on an outpatient basis.

The RECIST v. 1.1 criteria were used to assess the treatment results [21]. Volumetry was performed based on the assumption that the lesions were spherical. The focus volume was calculated according to the equation $V = \frac{4}{3}\pi r^3$, where V is the focus volume, and r is the focus radius. The calculation of the increase or decrease in the volume was performed according to the equation $\Delta V = \left| \frac{V_2 - V_1}{n_{\text{week}}} \times 100 \right|$, where ΔV is the increase or decrease in the focus volume, V_1, V_1 are the focus volumes in two consecutive studies, n_{week} is the number of weeks between studies.

The dynamics of changes in the tumor mass were assessed by calculating three parameters: a) $\Delta V_{\text{before/week}}$ (%) as the rate of increase in volume per week before the start of treatment; b) $\Delta V_{\text{treat/week}}$ (%) as the rate of volume decrease per week when a full or partial response to treatment is achieved; c) $\Delta V_{\text{prog/week}}$ (%) as the rate of increase in volume per week in the period between two studies, in one of which progression was stated, and the other preceded it. When developing a predictive model, the dynamics of the fastest-growing focus was considered. In the first line of therapy, all three parameters were calculated. In the second line, in some cases, in the absence of a free period between progression and the change in therapy, the values of parameters 1 and 3 coincided.

Clinical blood count and biochemical parameter determination were performed on a Cytomics analyzer using test systems and control materials from Beckton Dickinson. The biochemical analysis included evaluation of glucose, total protein, and albumin; nitrogenous compounds, namely urea, creatinine, uric acid; enzymes, such as alanine and aspartic transaminases, acid and alkaline phosphatases, lactate dehydrogenase; electrolytes, namely sodium, potassium, calcium, magnesium, chlorides; acute phase proteins, namely C-reactive protein, ceruloplasmin. Laboratory parameters were assessed before treatment initiation and then once every 10 days.

In the patients enrolled in the study, the lymphocyte content, their subpopulations, and cytokines were assessed in the blood:

1. Subpopulations of lymphocytes: $CD3^+CD16^-$ (mature T-lymphocytes, reference interval: $950–1800 \cdot 10^9$/l); $CD3^+CD8^+$ (cytotoxic lymphocytes, reference interval: $450–850 \cdot 10^9$/l); $CD3^+CD4^+$ (T-helpers, reference interval: $570–1100 \cdot 10^9$/l);

Table 2 / Таблица 2

Clinical characteristics of groups of patients with metastatic renal cell carcinoma
Клиническая характеристика групп пациентов с метастатическим почечно-клеточным раком

Parameter		Study group (n = 92)	Validation group (n = 261)
Gender	men	40 (43%)	89 (34%)
	women	52 (57%)	172 (66%)
Age	≤70 years	74 (80%)	233 (89%)
	>70 years	18 (20%)	28 (11%)
Karnofsky index	≤80%	18 (20%)	38 (15%)
	>80%	74 (80%)	223 (85%)
Histological type	clear cell	80 (87%)	173 (66%)
	non-clear cell	9 (10%)	12 (5%)
	unknown	3 (3%)	76 (29%)
Cytoreduction (nephrectomy, embolization)	yes	71 (77%)	167 (64%)
	no	21 (23%)	94 (36%)
Radiation therapy in history	yes	31 (34%)	47 (18%)
	no	61 (66%)	214(82%)
Diagnostics to the treatment period	≤12 months	78 (85%)	132 (51%)
	>12 months	14 (15%)	129 (49%)
MSKCC	favorable	19 (21%)	76 (29%)
	intermediate	61 (66%)	142 (54%)
	poor	12 (11%)	43 (17%)
Period of detection of metastases	synchronous	38 (41%)	112 (43%)
	metachronous	54 (59%)	149 (57%)
Localization of metastases	lungs	85 (92%)	132 (51%)
	lever	16 (17%)	26 (10%)
	bones	29 (32%)	71 (27%)
	lymph nodes	68 (74%)	131 (50%)
Anemia (hemoglobin <120 g/l)	yes	58 (63%)	168 (64%)
	no	34 (47%)	93 (36%)
Leukocytopenia ($<4 \cdot 10^9$/l)	yes	28 (30%)	72 (28%)
	no	64 (70%)	189 (72%)
Hypercalcemia (ionized calcium >1,4 mmol/l)	yes	6 (7%)	48 (18%)
	no	86 (93%)	213 (82%)
Platelets	$180–400 \cdot 10^9$/l	13 (12%)	126 (48%)
	$\geq 400 \cdot 10^9$/l	67 (77%)	114 (44%)
	$<180 \cdot 10^9$/l	12 (11%)	21 (8%)
LDH	≥230 U/l	31 (34%)	143 (55%)
	130–230 U/l	61 (56%)	118 (45%)
Creatinine	≥115 μmol/L	41 (45%)	132 (51%)
	50–115 μmol/L	51 (55%)	129 (49%)
Drug therapy	1 line	39 (42%)	212 (81%)
	2 lines	46 (50%)	45 (17%)
	3 lines and more	7 (8%)	4 (2%)

Note. MSKCC – Memorial Sloan-Kettering Cancer Center; LDH – lactate-dehydrogenase.

$CD4^+CD8^+$ (double-positive T-cells, reference interval: 5–15 · 10^9/l); $CD16^+CD56^+HLA\ DR^+$ (activated natural killer cells, reference interval: 18–150 · 10^9/l); $CD3^+CD16^+CD56^+$ (TNK-cells, reference interval: 5–200 · 10^9/l); $CD4^+CD25^+FoxP3$ (T-regulatory cells, reference interval: 0–110 · 10^9/l); $CD3^+HLA\ DR^+$ (activated T-cells, reference interval: 0–120 · 10^9/l); αβ-T (alpha/beta-T-cells, reference interval: 925–1625 · 10^9/l); γδ-T (gamma/delta-T-cells, reference interval: 20–115 · 10^9/l).

2. Cytokines (spontaneous production, SP; induced production, IP; concentration, C): interleukin 1β (IL 1, reference interval: SP 0–50 pg/ml; IP 1000–5000 pg/ml; C 0–50 pg/ml); interleukin 2 (IL 2, reference interval: SP 0–5 pg/ml; IP 10–100 pg/ml); interleukin 4 (IL 4, reference interval: SP 0–50 pg/ml; IP 100–400 pg/ml; C 0–50 pg/ml); interleukin 6 (IL-6, reference interval: SP 0–50 pg/ml; IP 1000–3000 pg/ml; C 0–50 pg/ml); interleukin 8 (IL-8, reference interval: SP 0–100 pg/ml; IP 1000–5000 pg/ml; C 0–50 pg/ml); interleukin 10 (IL-10, reference interval: SP 0–50 pg/ml; IP 100–400 pg/ml; C 0–50 pg/ml); interleukin 12 (IL 12, reference interval: SP 0–50 pg/ml; IP 100–600 pg/ml; C 0–50 pg/ml); interferon-α (IFN-α, reference interval: SP 0–50 pg/ml; IP 100–500 pg/ml; C 0–50 pg/ml); interferon-γ (IFN-γ, reference interval: SP 0–50 pg/ml; IP 1000–5000 pg/ml; C 0–50 pg/ml); tumor necrosis factor-α (TNF-α, reference interval: SP 0–50 pg/ml; IP 500–1500 pg/ml; C 0–50 pg/ml).

Analyses were performed in the immunological laboratory of the A.M. Nikiforov All-Russian Center for Emergency and Radiation Medicine of the Ministry of Emergency Management of Russia on a Cytomics FC500 laser flow cytometer (Beckman Coulter Inc., USA) using monoclonal antibodies and consumables manufactured by Beckman Coulter Inc., Immunotech S.A.S., Proteinovy Kontur, and Cytokine. Immune status was assessed before treatment and every 8–10 weeks during treatment.

On an outpatient basis, first-line study group patients received Sutent (sunitinib) 50 mg per day for eight weeks with an interval of two weeks (38 patients, 41%), and various options for chemoimmunotherapy (54 patients, 59%). The main chemoimmunotherapy options were two regimens: 1) Alfaron (recombinant IFN-α) nine million IU intramuscularly three times a week in combination with Avastin (bevacizumab) at a dose of 10 mg/kg intravenously once every 14 days; 2) Alfaron (recombinant IFN-α) nine million IU intramuscularly three times a week in combination with Refnot (recombinant TNF-α – thymosin α1) at a dose of 200,000 IU subcutaneously twice a week and Endoxan (cyclophosphamide) at a dose of 50 mg orally daily.

With progression during chemoimmunotherapy in the second line, the patients received 1) tyrosine kinase inhibitors (26 patients, 28%) in the form of Sutent 50 mg per day for eight weeks with an interval of two weeks, or Votrient (pazopanib) at a dose of 400–800 mg per day, depending on tolerance; 2) blockers of co-inhibiting molecules (11 patients, 12%) in the form of Opdivo (Nivolumab) 240 mg by intravenous infusion once every two weeks. With progression during the administration of Sutent, patients received Opdivo (five people, 5%) or other blockers of co-inhibiting molecules (four patients, 4%) as part of clinical trials.

In the validation group, the patients received various types of chemoimmunotherapy in the first and second lines, including drugs of recombinant interleukin 2, recombinant interferon-α, 5-fluorouracil, capecitabine, and cyclophosphamide [13–20]. Ten patients (4%) in the second-line validation group received Sutent (sunitinib) 50 mg per day for eight weeks with an interval of two weeks.

Statistical processing of the research results was performed using the Statistica version 10 software packages. Compliance of the sample parameters with the normal distribution criteria was assessed by calculating the arithmetic mean, median, kurtosis, asymmetry, and the Shapiro-Wilk test. The distribution was considered normal if the arithmetic mean value of the sample value was close to the median, the absolute values of kurtosis and asymmetry in modulus did not exceed 2, and the value of the Shapiro-Wilk test was significant and greater than 0.6. The influence of various parameters on the long-term treatment results was assessed using the logarithmic rank test and the Gehan-Wilcoxon test. The Cox proportional intensity regression model was used to identify the joint effect of several parameters on the lifetime indices.

RESULTS

At stage 1, a univariate analysis was performed to identify the parameters that significantly affect the long-term treatment results. At stage 2, multivariate analysis was performed to exclude components that act unidirectionally and equally. At stage 3, a predictive model was created.

The following parameters were chosen for univariate analysis:

1. Nominal: Karnofsky index, metastatic foci localization, cytoreductive intervention (nephrectomy, embolization), metastases detection period.

2. Continuous:

a) indicators of clinical and biochemical blood tests: hemoglobin, lactate dehydrogenase, ionized calcium, creatinine, leukocytes, platelets;

b) subpopulations of lymphocytes: $CD3^+CD16^-$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD4^+CD8^+$, $CD3^-CD16^+CD56^+$, $CD3^+CD16^+CD56^+$, $CD16^+CD56^+$HLA DR^+, $CD19^+$, $CD25^+$, $CD95^+$, $CD3^+$HLA DR, HLA DR^+, αβ-T, $CD4^+CD25^+$ Foxp3;

c) cytokines: IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-α, IFN-γ, TNF-α;

d) indices of tumor growth rate: $\Delta V_{before/week}$, $\Delta V_{treat/week}$, $\Delta V_{prog/week}$;

e) the time from the moment of diagnosis to the start of treatment.

The influence of various factors on long-term treatment results was assessed using the logarithmic rank test and the Gehan-Wilcoxon test.

As a result of univariate analysis, it was revealed that the following parameters influence progression-free survival rates:

1. Nominal: Karnofsky index ($p = 0.0006$), cytoreductive intervention ($p = 0.003$).

2. Continuous: hemoglobin ($p = 0.035$), platelets ($p = 0.027$), $CD3^+$HLA DR ($p = 0.0004$), $CD4^+CD25^+$ Foxp3 ($p = 0.038$), IL-6 (SP, $p = 0.007$, IP, $p = 0.032$), IL-8 (SP, $p = 0.008$, IP, $p = 0.042$), IL-10 (SP, $p = 0.0009$), TNF-α (SP, $p = 0.048$, IP, $p = 0.011$), $\Delta V_{before/week}$ ($p < 0.0001$), $\Delta V_{treat/week}$ ($p < 0.0001$), time from the moment of diagnosis to the start of treatment ($p = 0.004$).

A multivariate analysis was performed using the Cox proportional intensity regression model. This analysis enabled assessing the effect of a set of parameters and their contribution to survival rates, regardless of the nature of the sample's distribution. The multivariate analysis results are presented in Table 3. The predictive model parameters based on multivariate analysis are presented in Table 4.

The greatest contribution to the regression model is made by the level of spontaneous production of IL-10 (17.1%), IL-6 (15.7%), and the tumor volume reduction rate per week with a partial or complete response to treatment ($\Delta V_{treat/week}$, 15.6%). In contrast, the lowest is made by the level of platelets (11.1%). The influence of the regression model components on progression-free survival rates is presented in Table 5.

Spontaneous production of IL-6, IL-10, and $\Delta V_{treat/week}$ have the greatest discriminant ability. Their threshold values determine the maximum differences in survival rates between the groups.

Table 3 / Таблица 3

Results of multivariate analysis in the group of patients with renal cell carcinoma (progression-free survival)
Результаты многомерного анализа в группе пациентов с почечно-клеточным раком (выживаемость без прогрессирования)

Parameter	β	*k*, %	*M*	*Me*	95% CI	*p*
Clinical parameters						
Karnofsky index, %	0.003	13.2	–	0.001		
$\Delta V_{treat/week}$, %	0.002	15.6	–	0.036		
Diagnostics to the treatment period, months	–0.001	14.4	6.4	8.5	5.4–11.2	0.027
Laboratory parameters						
Hemoglobin, g/l	0.003	12.9	128	108	91–121	0.041
Platelets, $\times 10^{12}$/l	–0.002	11.1	380	365	348–515	0.048
IL-10, spontaneous production, pg/ml	0.002	17.1	380	450	256–480	<0.001
IL 6, spontaneous production, pg/ml	0.004	15.7	786	820	667–945	<0.001

Note. β – coefficient of the regression equation; *k* – coefficient of the parameter influence; *M* – arithmetic mean; *Me* – median; 95% CI – 95% confidence interval; $\Delta V_{treat/week}$ – rate of volume decrease per week when a full or partial response to treatment is achieved.

Table 4 / Таблица 4

Parameters of a predictive model based on multivariate analysis
Параметры прогностической модели, созданной на основе многомерного анализа

Parameter	Risk determining interval	RR	95% Cl	*p*
Clinical parameters				
Karnofsky index, %	>80 (+); ≤80 (–)	1.9	1.7–3.1	0.0007
$\Delta V_{treat/week}$, %	≤15 (+); >15 (–)	1.6	1.03–2.1	0.0005
Diagnostics to the treatment period, months	≤8 (+); >8 (–)	1.42	1.09–1.84	0.006
Laboratory parameters				
Hemoglobin, g/l	>108 (+); ≤108 (–)	1.67	1.31–1.92	0.021
Platelets, $\times 10^{12}$/l	≤350 (+); >350 (–)	1.42	1.19–2.01	0.012
IL-10, spontaneous production, pg/ml	≤400 (+); >400 (–)	2.1	1.82–3.21	0.0006
IL 6, spontaneous production, pg/ml	≤800 (+); >140 (–)	1.82	1.27–2.54	0.0004

Note. RR – risk ratio; 95% CI – 95% confidence interval; $\Delta V_{treat/week}$ – rate of volume decrease per week when a full or partial response to treatment is achieved.

Table 5 / Таблица 5

Influence of the parameters of the prognostic model on the results of treatment of patients with renal cell carcinoma in the study group
Влияние параметров прогностической модели на результаты лечения пациентов с почечно-клеточным раком в исследуемой группе

Prognostic model parameters		*Me* (95 % Cl), months	*p*
Karnofsky index, %	>80%	9.2 (7.1–10.1)	0.043
	≤80%	6.8 (5.4–7.9)	
$\Delta V_{treat/week}$, %	>15%	4 (3.1–5.3)	0.04
	≤15%	11.3 (9.8–12.1)	
Diagnostics to treatment period	>8 months	5.1 (4.4–6.8)	0.038
	≤8 months	9 (7.2–10.1)	
Hemoglobin	>108 g/l	10.8 (8.3–11.4)	0.03
	≤108 g/l	6.4 (5.8–7.8)	
Platelets	$\leq 350 \cdot 10^{12}$/l	12.1 (11.4–13.1)	0.008
	$>350 \cdot 10^{12}$/l	6.9 (5.9–7.7)	
IL-10, spontaneous production	>400 pg/ml	6.4 (5.2–8.6)	<0.0001
	≤400 pg/ml	12.8 (10.9–14.1)	
IL 6, spontaneous production	>800 pg/ml	4.4 (2.2–5.8)	<0.0001
	≤800 pg/ml	11.9 (9.6–12.9)	

Note. Me – median progression-free survival; 95% CI – 95% confidence interval; $\Delta V_{treat/week}$ – rate of volume decrease per week when a full or partial response to treatment is achieved.

Based on the model developed, 3 clinical groups were formed with a different number of risk factors: a) favorable prognosis with no risk factors, b) intermediate prognosis with 1–4 risk factors, c) poor prognosis with 5–7 risk factors. The progression-free survival rates in the study group and the validation group compared with the developed MSKCC model are presented in Table 6.

The developed model, compared with MSKCC, has a better discriminant ability. When MSKCC is used, in all studies, patients are in the intermediate prognosis group, whereas in the developed system, they are in groups with a favorable and poor prognosis. This tendency can be traced to both lines of treatment, both when using targeted and modern

Table 6 / Таблица 6

Long-term results of treatment of patients with metastatic renal cell carcinoma in the study group and in the validation group

Отдаленные результаты лечения пациентов с метастатическим почечно-клеточным раком в исследуемой группе и в группе валидации

Prognostic model			Study group		Validation group	
			I line	II line	I line	II line
Group as a whole		*n*	85	46	257	45
		Me, months	11.6	4.9	6.3	3.5
		95% CI	10.5–12.1	4.2–6.1	4.8–8.6	2.2–5.4
MSKCC	FP	*n*	14	4	51	7
		Me, months	12.2	6.2	8.2	4.8
		95% CI	10.9–13.2	5.5–7.1	7.5–9.6	3.1–6.2
	IP	*n*	63	34	161	27
		Me, months	11.8	5.2	6.1	3.2
		95% CI	9.8–12.7	3.4–7.8	5.5–6.9	1.8–5.2
	PP	*n*	8	8	45	11
		Me, months	6.1	2.8	4.2	2.6
		95% CI	4.3–8.2	1.5–4.2	3.5–4.8	1.2–4.8
A model with the inclusion of clinical, immunological parameters and parameters of the dynamics of the tumor mass	RF absents	*n*	24	11	73	11
		Me, months	14.1	8.1	10.4	6.8
		95% CI	13.1–15.2	6.5–10.1	9.8–10.9	4.8–7.3
	1–4 RF	*n*	45	23	103	18
		Me, months	8.2	4.8	4.2	4.1
		95% CI	7.6–8.9	2.9–5.3	3.7–5.1	2.9–5.8
	5–7 RF	*n*	16	12	81	16
		Me, months	4.8	2.1	2.3	2
		95% CI	4.2–5.1	1–3.6	1.5–2.8	1.2–4.7

Note. MSKCC – Memorial Sloan-Kettering Cancer Center; *Me* – median progression-free survival; CI – 95% confidence interval; FP – favorable prognosis; IP – intermediate prognosis; PP – poor prognosis; RF – risk factor; *n* – number of patients.

immune drugs, and in the validation group where cytokine therapy was performed, which indicates the universality of the developed model. Similar patterns are noted regarding treatment outcomes. In all subgroups studied, the median progression-free survival rate is higher with a favorable prognosis when using the developed model compared with MSKCC.

DISCUSSION

This study revealed that, in addition to traditional factors (Karnofsky index, time from the diagnosis to the start of treatment), cytokines (spontaneous production of IL-6 and IL-10), and one of the kinetic parameters, namely the rate of volume decrease per week upon reaching a complete or partial response to treatment also have prognostic potential.

Spontaneous cytokine production was studied in cultured lymphocytes. It reflects the range and intensity of production of low molecular weight regulators without stimulation. In cancer patients, this parameter indicates the degree of immune response disorganization. IL-6 and IL-10 are involved in the carcinogenesis processes and the immunosuppressive network formation.

IL-10 is a critical antitumor immune response regulator. The IL-10 family includes, in addition to the cytokine itself, IL-19, IL-20, IL-22, IL-24, and IL-26. It was isolated and characterized in 1989. Initially, it was called the cytokine synthesis inhibitory factor (CSIF). However, later it became apparent that it also possesses immunostimulating properties. In humans, the primary producers of IL-10 are T-regulatory cells, monocytes, tumor-associated macrophages, and tumor cells. The properties of IL-10 depend on the phase of interaction between the tumor and the immune system, the concentra-

tion of the cytokine, and the localization of its target cells. Its immunosuppressive effects are implemented in the lymphoid organs, whereas its immunostimulating ones are implemented in the tumor microenvironment. IL-10 inhibits dendritic cell maturation, which can become a source of IL-10 while generating T-regulatory cells in the tumor microenvironment. IL-10 inhibits proliferative activity and cytokine production by cytotoxic lymphocytes. Thus, IL-10 is involved in forming an immunosuppressive network, thereby contributing to disease progression. An increase in the IL-10 serum concentration, and genetic polymorphism of this cytokine, is associated with a poor prognosis of the disease [22, 23].

IL-6 is a cytokine with a wide range of biological activities, integrating the immune and neuroendocrine systems. Its main sources are T-lymphocytes, macrophages, myocytes, endotheliocytes, fibroblasts, and tumor cells. Under physiological conditions, it plays a central role in hematopoiesis and regulating the growth and differentiation of endotheliocytes, keratinocytes, osteoblasts, and neurons. In the immune system, IL-6 activates antibody proliferation and synthesis by B-lymphocytes, the proliferation of cytotoxic lymphocytes, stimulates the hematopoietic granulocytic lineage, and induces the expression of acute-phase proteins in the liver. The role of IL-6 in carcinogenesis has been intensively studied since the 1990s. It has been revealed experimentally that it can act as a paracrine or autocrine growth factor for many tumor types, including prostate cancer, kidney cancer, colorectal, hepatocellular carcinoma, and glioblastoma. Its high serum concentration contributes to the hyperactivation of the pituitary-adrenal system and the formation of a complex of pathological reactions, including depression that accompanies cancer. In addition, IL-6 is a pro-angiogenic factor and stimulates multidrug resistance gene expression [24, 25].

In this study, the volumetry of the foci was performed by calculation. A more accurate and modern method is automatic volumetry. However, this method currently has several disadvantages. In particular, due to the lack of a standardized methodology and a wide variety of software, it is difficult to achieve adequate reproducibility of studies. In addition, automatic volumetry limits the use of retrospective data [26].

The immediate prospects for the development of prognostic models of disseminated RCC are associated with the standardization of methods for assessment and interpretation of biomarkers and with the improvement of automatic volumetry of foci and assessment of the rate of change in the tumor mass volume [10, 12, 27–30].

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