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A Modern Approach to Diagnostics, Prediction and Course of Renal Cell Cancer

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ABSTRACT

Annually, about 295 thousand newly diagnosed cases of kidney cancer are registered in the world, and 134 thousand deaths from it. When analyzing the dynamics of epidemiological indicators over the past decades, an increase in the incidence of **Renal Cell Cancer(RCC)** was revealed, while mortality rates are significantly decreasing, especially in developed countries, which is associated with an increase in the use of medical imaging methods and the detection of small tumors (less than 4 cm), asymptomatic. ... At the time of diagnosis, RCC is detected at stage I in 45% of cases, locally advanced RCC in 33% of cases, and in 25% of cases, the tumor process is disseminated. Currently there are nomograms such asUCLA Integrated staging system (UISS), Stage Size Grade and Necrosis (SSIGN), integrated clinical and pathological prognostic scales for setting a prognosis, determining the duration and frequency of follow-up and determining a high-risk group in order to decide whether to conduct systemic therapy, however, they have a number of disadvantages and are in most cases intended for patients with metastatic RCC. Currently, the most common predictive model used for localized RCC is the Mayo Clinic's Integrated Staging System (UISS) and SSIGN. In connection with the above data, the development of new prognostic scales and nomograms with high accuracy and a personalized approach to the treatment of RCC patients based on risk categories are poorly understood problems and require in-depth study.

KEYWORDS

RenalCell Carcinoma (RCC),Nephrectomy, Thrombus, Renal Failure.

Introduction

Renal cell carcinoma**(RCC**) is a heterogeneous group of malignant tumors originating from tubular cells and ranks 10th in the world among cancers in terms of incidence [71]. It is interesting to note that 30% of patients after nephrectomy with primary RCC may subsequently develop metastases in distant organs [47,71,91]. According to the literature, the 5-year survival rate of RCC is 75%, with a direct dependence on the prevalence neoplastic process: with localized - 93%, regional - 70%, disseminated - 12% [47,71]. By its histological structure, the most common renal cancer is clear cell renal cancer, which, according to various authors, accounts for 70% to 85%, papillary cancer — 15%, chromophobic — 5% of cases [47,70]. It should be noted that recently the survival rate of RCC has been growing due to the discovery of the molecular genetic mechanisms of its development, as well as the development and implementation of new methods of treatment, in particular, immuno- and targeted therapy [58,70]. The risk of developing RCC increases with age in both men and women. According to the literature, the most significant established risk factors for the development of RCC are an increased body mass index, smoking, arterial hypertension, which are detected in almost half of the patients who applied for medical help. Also, the presence of chronic kidney disease, hemodialysis, kidney transplantation, early RCC, diabetes mellitus increase the risk of RCC, which has been confirmed in many epidemiological studies [9, 66]. Heredity also plays an important role in the development of RCC. It was found that in people in the family who had cases of RCC, the risk of its development increased by 2 times. In the study of cases of hereditary forms of RCC, mutations were found in at least 11 genes (BAP1, MET, FLCN, SDHB, FH, PTEN, SDHD, SDCH, VHLTSC1, TSC2). An example of this is the VHL gene mutation observed in Hippel-Lindau disease, which increases the risk of developing RCC, due to inactivation of the VHL protein, which leads to uncontrolled expression of the oncogenic factors HIF-1 and HIF-2 [8]. Also, in connection with the progress in the field of molecular biological and molecular genetic research, the informative value of immunohistochemical and genetic research methods is increasing today, the results of which allow a differentiated approach to the treatment and prognosis of patients with RCC, as well as the correct histological

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diagnosis [8,26,48.51.70]. The most important markers in the diagnosis of renal neoplasms are **cytokeratins, vimentin, PAX2, RCC markers, PAX8, E-cadherin, CD10, renal-specific cadherin, parvalbumin, claudin-7, claudin-8, CD117, TFE3, thrombomodulin, p63, uroplakin CD57** et al [7,8,77]. Each of the above antibodies plays a specific role in the histological diagnosis and differential diagnosis of RCC from other tumors of nonrenal cell origin, as well as rare histological forms. In molecular genetic prediction of **RCC, markers such as hypoxia-induced factor-a (HIFa), VEGF, CAIXb p53, ki67, CXCR3, insulin-like growth factor II, IMP3, B7-H1, survivin, PD-1, PD -L1, KIT, mTOR** et al [8,12,46,39,76,61]. Alternatively, algorithms based on large-scale gene expression profiling by using the Cancer Genome Atlas (TCGA, https://cancergenome.nih.gov), which have been used to predict tumor purity in many studies [41,48,51, 60.62.73]. The ESTIMATE algorithm (Evaluation of stromal and immune cells in the tissues of malignant tumors by expression data) allows determining the level of infiltrating stromal and immune cells by calculating stromal and immune parameters [81].

The choice of the volume of surgical intervention depends on the stage of the disease and the general condition of the patient [28,30]. According to international recommendations, indications for kidney resection in RCC are T1, cancer of a single kidney (anatomical or functional), bilateral RCC, Hippel-Lindau syndrome [28,30,70]. Renal failure refers to relative indications for organ-preserving operations. Studies have shown that when comparing long-term results of treatment by renal resection and nephrectomy in RCC T1, they had identical values with less effect on renal function [70]. The question of the need and volume of regional lymph node dissection is still the subject of research [4,21,23,50,78,79]. In order to avoid potential complications, it is necessary to carefully approach the issue of patient selection. However, only the use of an adequate volume of surgical intervention can achieve good treatment results with a 5-year overall survival rate of 40 to 65% in RCC patients without distant metastases [17,96,118]. According to the studies, the efficiency of cryodestruction and radiofrequency ablation was 89% and 90%, respectively, with a complication rate of 20% and 19%. When studying the literature, it was revealed that protocols for the follow-up of RCC patients based on the risk category have not been fully developed [43,70]. Traditionally, RCC is resistant to PCT, and therefore the prognosis of patients for a long time remained disappointing, however, with the development of new drugs for immunotherapy and targeted therapy for RCC, an improvement in treatment results began [1,6,10,40,44.58,64,69]. The choice of treatment tactics for RCC is based on the clinical efficacy of targeted drugs, possible side effects, the presence of comorbidities, and the general condition of the body. Nevertheless, due to the rapid development of modern drugs, the issue of choosing a particular drug presents significant difficulties and serves as the subjects of clinical research [11,14,16,19,22,35]. To date, there are a number of studies of the use of anti-VEGF with immunotherapeutic drugs of a new generation, both alone and in combination with tyrosine kinase inhibitors, inhibitors of immune checkpoints of T-lymphocytes, such as antibodies against ligands of protein-1 programmed cell death (PD-L1- avelyumab, atezolizumab) and protein-1 programmed cell death (PD-1nivolumab, pembrolizumab), cytotoxic T-lymphocyte associated protein 4 (CTLA-4-ipilimumab) [32,101]. The PI3-K / Akt / mTOR pathway plays a central role in cell proliferation and maintenance of homeostasis, which is activated in many malignant tumors [27,84,46,59,84]. Allosteric mTOR inhibitors have shown promising activity in the treatment of progressive RCC and two such agents, temsirolimus and everolimus, are now approved as first and second line treatments for metastatic RCC. Studies of the complex PI3-K / Akt / mTOR pathway and its regulation have revealed several mechanisms of resistance to mTORC1 inhibitors and provided a basis for the development of new agents (i.e. direct mTOR kinase inhibitors or dual PI3-K / mTOR inhibitors) and new combination strategies that can lead to greater clinical efficacy [27,84,46,59]. Given the many developed therapeutic agents for RCC, efforts should be directed towards identifying predictive biomarkers of response to currently available mTORC1 inhibitors and new targeting agents [27,84,46,59]. It should be noted that the majority of works are devoted to studies of the effectiveness of immuno- and targeted therapy in metastatic RCC [6,27,32,35,44,58,61,64,69]. At the same time, the effectiveness of the use of immunotherapeutic and targeted drugs in the adjuvant mode has not been sufficiently studied and the results of the conducted studies are contradictory [37,54,55,57,58,70]. For example, in the ASSURE randomized trial comparing sunitinib, sorafenib, and placebo, there was no improvement in disease-free and overall survival in RCC patients. To date, VEGF and mTOR pathways are potentially significant prognostic and predictive markers [18,46,54]. Angiogenesis marker VEGF is represented by 4 different isoforms, the expression of which is also independently associated with the survival of patients with RCC. An alternative method for detecting PD-L1, such as flow cytometry, could more accurately characterize the presence of ligand isoforms. Although most studies have used anti-PD-1 drugs, they have focused on the expression of the PD-L1 ligand rather than the PD-1 receptor. PD-1 expression in tumor infiltrating lymphocytes was not associated with negative clinical outcomes.

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The aim of the study was to improve treatment outcomes for patients with RCC by developing a personalized approach based on predictive risk categories.

Research Materials and Methods

To study the cause of the factors that led to the generalization of the neoplastic process, the peculiarities of the clinical course of the disease in patients with RCC, a retrospective analysis was performed of 150 patients with T1-4N0-1M0 who had previously undergone surgical treatment in the conditions of Tashkent oncological Center from 2011 to 2019. The division of patients into groups was as follows: the first group included 70 patients with RCC after radical treatment during dynamic follow-up in whom the progression of the oncological process was observed, the second group - 80 patients with RCC who did not develop relapse and distant metastases for 5 years. In terms of age in the study, the age ranged from 31 to 83 years. The average age of the patients was 57 ± 10.5 years. The distribution between the groups by gender and age was even.The study included 74 (49.3%) men and 76 (50.7%) women. Upon admission, all patients underwent a standard comprehensive examination for RCC, including both general clinical and special research methods. On the basis of postoperative pathological material, all patients established the extent of the oncological process, the histological structure of the tumor and its other important pathological parameters, as well as the status of the lymph nodes.

The Criteria for Inclusion in the Research Were

- Histologically confirmed primary renal cell carcinoma of the kidney
- Absence of metastases in distant organs
- Performed surgical intervention

The Exclusion Criteria from the Study Were

- Primary multiple tumors
- Bilateral kidney cancer
- Refusal to carry out surgery
- The presence of distant metastases

A palpable mass was a common local symptom (41% of cases). There were also symptoms such as pain in the lumbar region (47.3%) and hematuria (26%). General weakness (78.7%) and loss of appetite (70.7%) were common symptoms that were more common in the patients included in the study. The tumor almost equally affected both the right (56%) and left (44%) kidneys. From palpation data, such characteristics of the tumor as consistency and its mobility were investigated. Of 71 patients with palpable lesions, in 48 (67.6%) cases, the tumor was dense in consistency, in 23 (32.4%) cases, soft. According to the parameter of mobility in cases of 26 (17.3%) moderately mobile, 32 (21.3%) inactive in cases, immobile in 13 (8.6%) cases, the tumor was not palpable in 79 (52.6%) cases. The period from the onset of symptoms to hospitalization ranged from 1 to 12 months. Most of the patients included in the study were I and II (38% and 26.7%, respectively), while patients with stage III of the disease accounted for 18.7%, and with stage IV in 16.7% of cases. The vast majority of patients had clear cell carcinoma (85.3%), the most rare histological type of RCC was oncocytic renal cancer (0.67%).

Table 1. Patient characteristics

Characteristic	Total (n=150)	Main group (n=70)		Control group (n=80)		χ2	P
		Абс	%	Абс	%		
Symptoms:							
Lumbar pain	71	35	50	36	45	0,374	>0,05
The presence of a palpable mass	62	41	58,6	21	26,25	16,084	<0,001
Hematuria	39	25	35,7	14	17,5	6,437	<0,01
Lack of appetite	106	61	87,1	45	56,25	17,188	<0,001
General weakness	118	68	97,1	50	62,25	26.698	<0,001
Localization of the tumor:							

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Right kidney	84	38	54,3	46	57,5	0.157	>0,05
Left kidney	66	32	45,7	34	42,5	0,157	>0,05
Upper	42	25	35,7	17	21,25	3,874	<0,05
Rear	5	3	4,3	2	2,5	0,369	>0,05
Middle	27	10	14,3	17	21,25	1,227	>0,05
Lower	31	7	10	24	30	9,108	<0,01
Defeat of 2 segments	33	15	21,4	18	22,5	0,025	>0,05
Total defeat	12	9	12,9	3	3,75	4,207	<0,05
Disease stage (classification 8):							
I	57	12	17,1	45	56,25	24,234	<0,001
II	40	17	24,3	23	28,75	0,38	>0,05
III	28	23	32,9	5	6,25	17,408	<0,001
IV	25	18	25,7	7	8,75	7,736	<0,01
Tumor size:							
Less than 4 cm	26	7	10	19	23,75	4,926	<0,05
4-7 cm	62	25	35,7	37	46,25	1,71	>0,05
7-10 cm	50	29	41,4	21	26,25	3,871	<0,05
More than 10 cm	12	9	12.9	3	3,75	4,207	<0,05
Accompanying illnesses:							
Diseases of the gastrointestinal tract	96	47	67,1	49	61,25	0,563	>0,05
CVS diseases	106	61	87,1	45	56,25	17,118	<0,001
MPS diseases	83	45	64,3	38	47,5	4,256	<0,05
Endocrine system diseases	68	38	54,3	30	37,5	4,245	<0,05
Severity of comorbidity according to ACE 27							
No	40	13	18,57	27	33,75	4,398	<0,05
Easy	57	19	27,1	38	47.5	6,567	<0,01
Average	31	23	32,9	8	10	11,896	<0,001
Heavy	22	15	21,4	7	8,75	4,795	<0,05

Table 2. Characteristics of the tumorproces

Factors	**Total (n=150)**	**Main group (n=70)**		**Control group (n=80)**		**χ2**	**P**
		Абс	**%**	**Абс**	**%**		
TNM classification of primary tumor:							
T1a	24	5	71,4	19	23,75	7.661	<0,01
T1b	36	10	14,3	26	32,5	6,79	<0,01
T2a	38	16	22,9	22	27,5	0,425	>0,05
T2b	9	6	8,6	3	3,75	1,539	>0,05
T3a	27	21	30	6	7,5	12,805	<0,001
T3b	10	8	11,4	2	2,5	4,783	<0,01
T3c	3	2	2,9	1	1,25	0,492	>0,05
T4	3	2	2,9	1	1,25	0,492	>0,05
Lymph node status:							
N0	128	55	78,6	73	91,25	4,795	<0,05
N1	22	15	21,4	7	8,75	4,795	<0,05
Histological structure:							
clear cell	128	65	92,85	63	78,75	5,936	<0,05
papillary (chromophilic)	10	1	1,43	9	11,25	5,788	<0,05
chromophobic	5	0	0	5	6,25	4,526	<0,05
Oncocytic	1	1	1,43	0	0	1,151	>0,05
Sarcomatous	6	3	4,3	3	3,75	0,028	>0,05
Differentiation degree:							
G I	30	12	17,1	18	22,5	0,67	>0,05
G II	52	15	21,5	37	46,2	10,16	<0,01
G III	39	24	34,3	15	18,8	4,68	<0,05
G IV	29	19	27,1	10	12,5	5,133	<0,05
Lymphovascular invasion							
Yes	49	34	48,6	15	18,75	15,09	<0,001
No	101	36	51,4	65	81,25	15,09	<0,001

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Infiltration of the tumor with lymphocytes							
Yes	47	29	41,4	18	22,5	6.217	<0,01
No	103	41	58,6	62	77,5	6.217	<0,01
Parenchyma to tumor stroma ratio							
Pronounced stroma	44	15	21,4	29	36,25	3,956	<0,05
Lean stroma	106	55	78,6	51	63,75	3,956	<0,05

Comprehensive study of RCC patients included laboratory and instrumental studies (general and biochemical blood tests, coagulogram), ultrasound, excretory urography, MSCT and MRI studies, histological examination of postoperative material.

Table 3. Ultrasound characteristics of RCC depending on the prognostic group

Parameter	**Main group (n=70)**		**Control group (n=80)**		**Total (n=150)**	
	Абс	**%**	**абс**	**%**	**абс**	**%**
Ultrasound structure						
Homogeneous	11	15,7	23	28,75	34	22,7
Heterogeneous	59	84,3	57	71,25	116	77,3
Ultrasound contours						
Clear	7	10	38	47,5	45	30
Fuzzy	63	90	42	52,5	105	70
Ultrasound form						
Oval	9	12,86	13	16,25	22	14,7
Round	14	20	17	21,25	31	20,7
Wrong	47	67,1	50	62,5	97	64,7
Signs of hydronephrosis						
there is	61	87,1	45	56,25	106	70,6
On the defeat side	45	64,3	40	50	85	56,7
On the contralateral side	16	22,9	5	6,25	21	14
No	9	8,6	35	43,75	44	29,3

Ultrasound examination was performed on the Toshiba-xario-200 apparatus using a 7.5 MHz linear transducer according to the standard technique. In the process of ultrasound, the position, shape and structure of the kidneys were assessed, both in general and separately, of various structures, such as the parenchyma of the kidney, renal sinus and its elements, according to such indicators as echogenicity and echostructure. In addition, the state of perirenal tissue and the status of lymph nodes were assessed. In addition to ultrasound of the kidneys, the abdominal and pelvic organs were assessed for the presence and absence of distant metastases.

Table 4.X-ray signs on excretory urography depending on the prognostic group

X-ray signs	**Main group (n=70)**		**Control group (n=80)**		**Total (n=150)**	
	Абс	**%**	**абс**	**%**	**абс**	**%**
deformation of the contours of the cup-pelvis system	53	35,3	64	42,7	107	71,3
disorganization of the typical calyx arrangement	37	52,9	48	32	95	63,3
calyx amputation	25	35,7	9	6	34	22,7
an increase in the distance from the edge of the calyx to the outer contour of the kidney	45	30	42	28	87	58
dumb kidney	18	12	6	4	24	16

Excretory urography was used to assess the functional state of the kidneys and urinary tract, by administering an iodine-containing contrast agent intravenously and taking pictures at 5-7, 12-15 and 20-25 minutes of the study. With excretory urography, conclusions can be drawn about the state of the accumulative and excretory function of the kidneys, the presence or absence of signs of obstruction, deformation of the calyceal-pelvic system. Multislice

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computed tomography was performed on the "Aquilion One - 640" version of GENESIS (Canon Medical Systems, Japan) in order to identify the volumetric formation of the kidney, the degree of local and distant spread of the process, to assess the anatomical features of the structure of the vascular system and urinary tract, the status of regional lymph nodes, as well as planning the scope of surgical intervention. During the MSCT study, the following MSCT scanning protocols were used: for native examination - 120 kV, 200 mAs; during dynamic examination - 100 kV, 100-450 mAs (depending on the weight of the subject). In order to optimize the preparation of the histological material, the tissue matrix technique proposed by S.J. Choi et al. Was used, for which 150 histological blocks (donor blocks) of RCC patients included in our study were used, implanted on 2 tissue matrices. The tissue matrix fabrication technology included the following stages: careful organization of the study, preparation of the recipient block and donor blocks, planning and creation of a matrix map, sampling from the donor block and implantation of histological material into the recipient block.

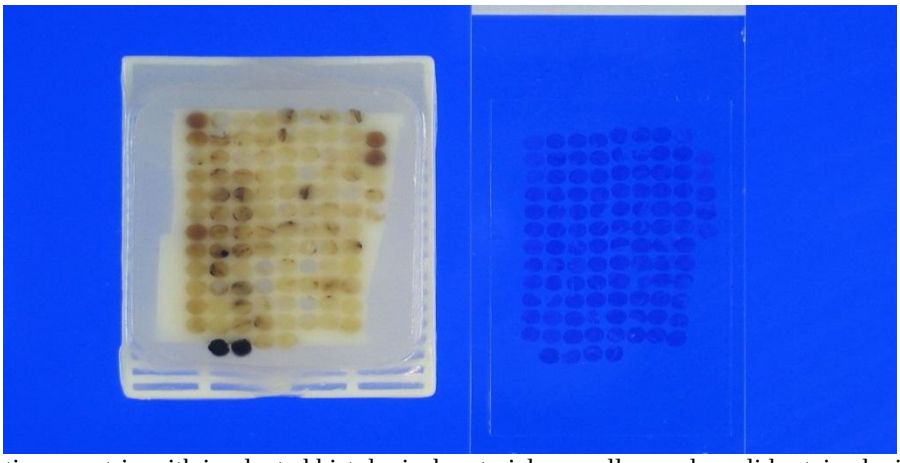

Figure1. Ready tissue matrix with implanted histological material, as well as a glass slide stained with hematoxylin-eosin.

The stages of the immunohistochemical study included dewaxing of tissue sections and their rehydration, antigen unmasking by applying protein kinase K and incubation for 5-10 min, followed by washing with distilled water and placing in TBS, placing in a solution for unmasking the antigen, heating in a water bath for 25-40 min at a temperature of 95-99 degrees, cooling at room temperature for 20 minutes, rinsing with distilled water and placing in TBST at a pH of 7.6, the actual process of staining with a monoclonal antibody to the receptor, dehydration and stabilization with a filling medium, study of the obtained micropreparations. The following antibodies for IHC staining were used: PD-1 / PD-L1, mTOR, VEGF-A and KIT, high proliferation index.

An integral method of treating RCC is surgery in the volume of a kidney resection or nephrectomy. Radical nephrectomy is the gold standard for renal cell carcinomas when renal resection is not possible. Radical nephrectomy involves removing the kidney along with the fat capsule, Gerot's fascia, and regional lymph nodes. The transperitoneal approach is optimal for radical nephrectomy, which allows adequate control of the renal vessels. Adrenalectomy was performed only in the presence of large tumors of the upper pole of the kidney. If a venous tumor thrombosis was detected, it was removed. Lymphatic dissection in left-sided tumor location consisted of removal of para-aortic and aortocaval groups of lymph nodes; in right-sided tumors, intra-aortocaval, retrocaval, laterocaval, aortocaval, and precaval groups of lymph nodes were removed. When carrying out organ-preserving operations on the kidneys, the general principles of surgical intervention were: control over the vessels of the kidneys, minimization of the time of ischemia of the renal parenchyma, removal of the formation within healthy tissues, hermetic suturing of the collecting renal system, and closure of the renal parenchyma defect with various kinds of flaps.

Table 5. Characteristics of surgical treatment

Surgical method	Group I (n=70)	GroupII (n=80)	Total

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	абс	%	Абс	%	абс	%
Radical nephrectomy	45	64,3	65	81,25	110	73,3
Extended nephradrenectomy	21	30	8	10	29	19,3
Kidney resection	4	5,7	7	8,75	11	7,4

In most cases, radical nephrectomy was performed (73.3%). When the tumor is located in the upper pole and grows into the adrenal gland, radical nephrectomy was complemented by adrenalectomy (19.3%). In 7.4% of cases, kidney resection was performed.

One of the main stages of radical nephrectomy is a standard lymph node dissection, which involves the removal of regional lymph nodes.

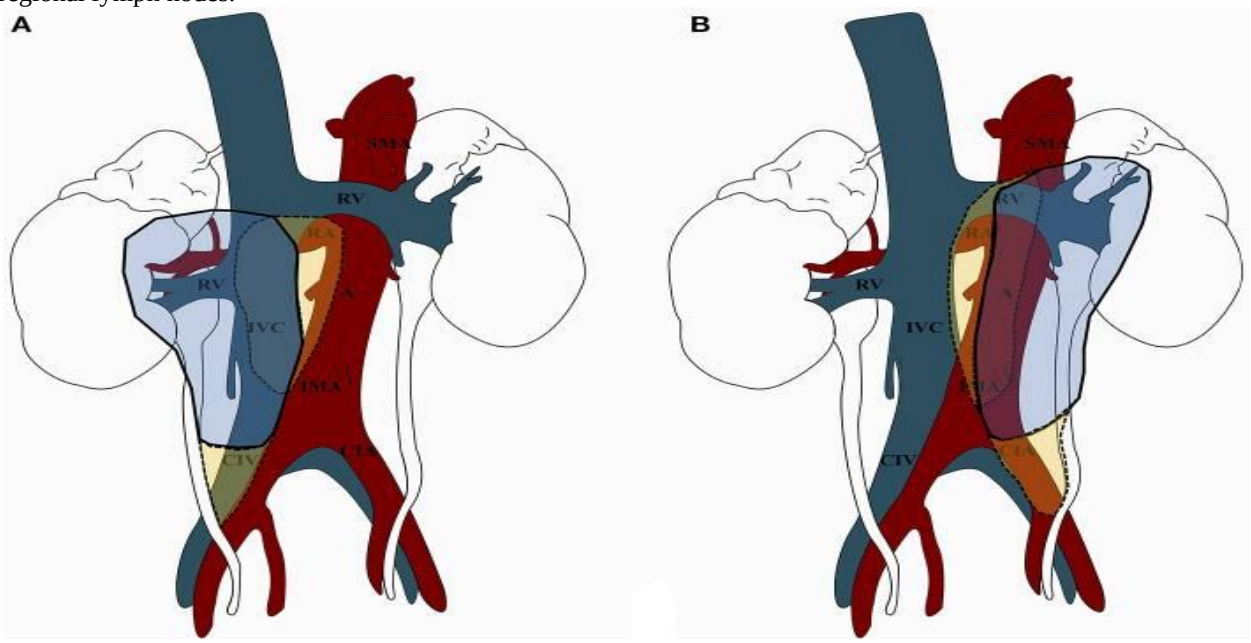

Fig. 2. Schematic representation of different types of lymphadenectomy: in right-sided tumors (A), standard lymphadenectomy is indicated in blue. Extended lymph node dissection borders are outlined with a dotted line. A, aorta; CIA, common iliac artery; CIV, common iliac vein; IMA, inferior mesenteric artery; IVC, inferior vena cava; RA, renal artery; RV, renal vein; SMA, superior mesenteric artery. (Adapted from Campi, Riccardo et al. "Templates of Lymph Node Dissection for Renal Cell Carcinoma: A Systematic Review of the Literature." Frontiersinsurgery vol. 5 76).

Table 6. Distribution of RCC patients depending on the volume of lymph node dissection

Lymph node dissection type	Group I (n=70)		GroupII (n=80)		Total	
	абс	%	Абс	%	абс	%
Selective	24	34,3	21	26,25	45	30
Extended	21	30	47	58.75	68	45,3
Not performed	25	35,7	12	15	37	24,7

In order to plan a surgical intervention in the presence of a tumor thrombus, the classification of the Mayo Clinic was used, according to which there are 4 levels of prevalence of an intravascular thrombus.

Table 7. Classification of tumor thrombi and surgical tactics, according to the classification of the Mayo Clinic

Level	Description	A Surgical Approach to Achieve Tumor Thrombus Control	
0	Limited to the renal vein or its tributaries	Renal vein ligation	

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I	Spreads into the inferior vena cava, but <2 cm above the renal vein orifice	Extrusion of a tumor thrombus from the inferior vena cava into the renal vein, followed by ligation of the renal vein	
II	Distributed into the inferior vena cava> 2 cm above the renal vein orifice but below the hepatic veins	Some liver mobilization (ligation of auxiliary hepatic veins draining the caudate), clamping the intrahepatic inferior vena cava, infrarenal inferior vena cava, and contralateral renal vein	
III	Spreads above the hepatic veins but below the diaphragm	Extensive liver mobilization, including ligation of the legs of the diaphragm, clamping of the suprahepatic inferior vena cava with accessory venovenous or cardiopulmonary collaterals	
IV	Spreading above the diaphragm	Involvement of thoracic surgeons, possible thoracotomy and open heart surgery	

Immunotherapy treatment. For the purpose of immunotherapy among the high-risk group, Roferon-A was used in a dosage regimen of 3 million IU intramuscularly 1 time per day for 10 days, with intervals between courses for 21 days.

Targeted therapy. Patients with VEGF-A receptor expression were treated with standard dosing bevacizumab and sorafenib.

The severity of comorbidities was assessed using the 27-step Adult Comorbidity Evaluation-27 (ACE-27) scale used in cancer patients. Comorbidity was defined as a pre-existing medical condition present at the time of diagnosis of RCC. In the ACE-27 rating scale, diseases are divided into one of three levels of severity (none, mild, moderate, or severe) depending on the level of decompensation of individual organs and prognostic value. According to the classification of individual diseases, the total comorbidity score is classified as no comorbidity, mild, moderate, or severe comorbidity. The score was calculated automatically using the online calculator https://www.medicalalgorithms.com/comorbidity-scores-cancer.The ECOG Common Toxicity Criteria classification (2nd edition 1999) was used to assess toxic effects.

The assessment of the general condition of patients was carried out on the basis of the Karnovsky and ECOG scales. Dynamic control in RCC is aimed at assessing and identifying postoperative complications, renal functional state, early diagnosis of local recurrence and distant metastases.
The arsenal of diagnostic procedures for the purpose of dynamic observation included: standard urine and blood tests, ultrasound of the abdominal cavity and small pelvis, chest fluoroscopy, CT of the abdominal cavity and small pelvis (once a year).

For the purpose of statistical analysis of the data, the IBMSPSS 18 program was used. The initial stage of statistical data processing was the identification of the predictive value for the outcome of the neoplastic process, the studied features by creating contingency tables. The methods of statistical analysis used in the study were: to identify common predictive factors - factor analysis with the calculation of the specific weight of the trait separately, and its effect on the outcome; to determine the presence or absence of a relationship between the predictive factors, nonparametric correlation analysis was used according to the Candell method; in order to determine the differences between the signs - Fisher's angular transformation criterion, relative risk criterion, Pearson's goodness-of-fit criterion ($\chi 2$). The reliability of statistical differences was characterized as high at $p < 0.001$, average at $p < 0.01$, marginal at $p < 0.05$, insignificant at $p > 0.05$.

The analysis of disease-free and overall survival was carried out using the Kaplan-Meier method. In order to create a predictive nomogram, the maximum likelihood method was used. The essence of the method is to determine the probability of the appearance of each feature in each of the groups under study. The calculation of probability indicators is carried out according to the formula, in which m is the number of observations of a feature in the studied group, N is the total number of observations. According to the likelihood ratio formula, the specific weight of the putative prognostic trait is calculated and is represented by the formula ln (P1 / P2), where P1 is the probability of the appearance of the trait under study in a group with a poor outcome, P2 is the probability of the appearance of the trait under study in a group with a favorable outcome. The value of the final forecast index (Z), which determines the individual forecast, is determined by summing the weight coefficients of all studied signs, according to which, with a

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value of Z≥0, the observation belongs to the prognostically favorable group, Z <0 to the poor forecast group.

Results

When analyzing the effect of the existing symptoms on the prognosis of the disease, it was found that the most unfavorable among them were general symptoms, such as general weakness and loss of appetite, which are possibly associated with the biological activity of the tumor, and were more often observed in the group with a poor prognosis (87.1%, 97.1% and 56.25 and 62.25%, respectively; p <0.001).

Table 8. Distribution of clinical symptoms among prognostic groups of RCC

Characteristics	Total (n=150)		Main group (n=70)		Control group (n=80)		χ2	P
	Абс	%	Абс	%	Абс	%		
Lumbar pain	71	47,3	35	50	36	45	0,374	>0,05
The presence of a palpable mass	62	41,3	41	58,6	21	26,25	16,084	<0,001
Hematuria	39	26	25	35,7	14	17,5	6,437	<0,01
Lack of appetite	106	70,7	61	87,1	45	56,25	17,188	<0,001
General weakness	118	78,7	68	97,1	50	62,25	26.698	<0,001

There was also a direct correlation between the symptoms of general intoxication, the prevalence of the process and the degree of tumor necrosis (p <0.001).

Other symptoms such as the presence of palpable mass and hematuria were less common than general symptoms, while there was a statistically significant difference in prevalence between groups (58.6%, 35.7% and 35.7% and 17.5%, respectively; p <0.001).

The duration of the medical history also influenced the outcome of the disease. In patients with a short history and a rapid development of clinical symptoms, the course of the disease was more aggressive, which may have been associated with a rapid tumor growth, while a longer history indicates a more favorable prognosis. At the same time, a relationship was also noted between the severity of symptoms and the degree of spread of the oncological process and the localization of the primary tumor, its germination into the capsule, adjacent organs and structures.

Table 9. Correlation analysis between the presence and severity of comorbidity and the outcome of RCC

Parameter and degree	Total (n=150)		Main group (n=70)		Control group (n=80)		χ2	P
	абс	%	абс	%	абс	%		
Accompanying illnesses:								
Diseases of the gastrointestinal tract	96	64	47	67,1	49	61,25	0,563	>0,05
CVS diseases	106	70,7	61	87,1	45	56,25	17,118	<0,001
MPS diseases	83	55,3	45	64,3	38	47,5	4,256	<0,05
Endocrine system diseases	68	45,3	38	54,3	30	37,5	4,245	<0,05
ACE severity of comorbidity								
No	40	26,7	13	18,57	27	33,75	4,398	<0,05
Easy	57	38	19	27,1	38	47.5	6,567	<0,01
Average	31	20,7	23	32,9	8	10	11,896	<0,001
Heavy	22	14,7	15	21,4	7	8,75	4,795	<0,05

Due to the fact that RCC patients belong to the elderly or senile age group, the vast majority of the studied had concomitant diseases, which in turn also influenced the choice of treatment tactics and the outcome of the disease. Comorbidity is defined as any coexisting disease or condition that can affect the diagnosis, treatment, and prognosis of a disease.

As can be seen from our analysis, there is a clear prognostic gradient for patients with severe comorbidities (χ2 =

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4.795, p <0.05). As a result of the correlation analysis, it was revealed that the overall relationship between the severity of comorbidity and survival is significant. Also, in patients with the absence or presence of mild concomitant pathology, the course and outcome of the oncological process are more favorable ($\chi2$ = 4.398, p <0.05 and $\chi2$ = 6.567, p <0.01, respectively).

At the same time, it is interesting to note that in group I, compared with group II, diseases of the cardiovascular (87.1% and 56.25%, respectively), urogenital (64.3% and 47.5%, respectively) and endocrine systems (54.3% and 37.5%, respectively).

When analyzing indicators of a general blood test, statistically significant parameters influencing the outcome of the disease were a change in the number of platelets upward, as well as a decrease in the level of erythrocytes and hemoglobin, which was reflected in the differences between these indicators in the comparison groups.

According to our study, thrombocytosis negatively affected the rates of relapse-free and overall survival and was more often associated with the development of relapses and metastases, which could be due to increased paraneoplastic activity of tumors. In patients of group I, a shift in the number of platelets towards an increase was observed in 30% of cases, while in group II, only in 13.75%. It is known that platelets have a protective effect on tumor cells released into the bloodstream, by entering into a relationship with them, as well as a stimulating effect on malignant cells, through the release of growth factors VEGF, PDGF, thrombospondin, etc. Statistical analysis showed that thrombocytosis is independent an unfavorable prognosis factor in RCC.

Table 10. Changes in blood and hemostasis parameters and their impact on the prognosis of RCC

Parameter	**Total (n=150)**		**Main group (n=70)**		**Control group (n=80)**		**χ2**	**P**
	абс	**%**	**абс**	**%**	**абс**	**%**		
Thrombocytosis								
Yes	32	21,3	21	30	11	13,75	5,874	<0,05
No	118	78,7	49	70	69	86,25	5,874	<0,05
Anemia								
Yes	106	70,7	65	92,9	41	51,25	31,179	<0,001
No	44	29,3	5	7,1	39	48,75	31,179	<0,001
Hemostasis disorders								
Hypercoagulation	68	45,3	39	55,7	29	36,25	5,707	<0,05
Hypocoagulation	23	15,3	11	15,7	12	15	0,015	>0,05
Normocoagulation	59	39,4	20	28,6	39	48,75	6,307	<0,05

In addition, anemia was a factor negatively affecting the course and outcome of RCC, which was mostly found in the poor prognosis group, 92.9% and 51.25%, respectively (p <0.001). It should be noted that hypoxia is an important factor inducing the defense mechanisms of malignant cells. At a low content of intercellular oxygen, a high expression of HIF-is observed, the accumulation of which stimulates the processes of angiogenesis, drug resistance, and tumor progression. Based on the analysis of the data, a correlation was found between anemia and poor outcome in RCC.

Disruption of the blood coagulation and anticoagulation systems is associated with the production of biologically active substances by malignant cells. In our study, it was found that violations of hemostasis in the direction of both hypo- and hypercoagulation were associated with an increased risk of metastasis, which may be associated with an increased release of tumor cells into the bloodstream with an increase in fibrinolytic activity, while hypercoagulation leads to formation and delay of tumor thrombi, which is the starting point of the final stage of metastasis ($\chi2$ = 5.707; p <0.05).

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Based on the analysis, a direct relationship was revealed between the development of relapse or metastasis with such indicators as the size and prevalence of the primary tumor to adjacent organs and structures, the presence of a tumor thrombus, the presence of metastases in regional lymph nodes, and the stage of the disease.

It is also interesting to note the influence of the type of tumor thrombus on the prognosis of RCC. With a freely floating thrombus, the outcome was significantly better than with thrombi that grow into the wall of the inferior vena cava. Also, an unfavorable prognosis was associated with tumor invasion into the perirenal tissue of the kidney.

With a locally advanced process with invasion into the spleen and other structures, the prognosis of the disease is also unfavorable. The average duration of the relapse-free period was 9.3 months.

Table 11. Distribution of the prevalence of the tumor process on adjacent organs and structures between prognostic groups

Parameter	**Total (n=150)**		**Main group (n=70)**		**Control group (n=80)**		**χ2**	**P**
	Абс	**%**	**абс**	**%**	**Абс**	**%**		
Tumor thrombus								
Yes	36	24	27	38,6	9	11,25	15,278	<0,001
No	114	76	43	61,4	71	88,75	15,278	<0,001
Localization of a tumor thrombus								
Renal vein	23	15,3	12	17,1	11	13,75	0,331	>0,05
Below aperture level	13	8,7	10	14,3	3	3,75	5,235	<0,05
Above aperture level	0	0	0	0	0	0	0	0
Germination of a tumor to adjacent organs								
Paranephrium	3	2	2	2,9	1	1,25	0,492	>0,05
Adrenal gland (by the number of adrenalectomies	29	19,3	21	30	8	10	9.575	<0,01
Adrenal gland (T3 / T4)	12	8	9	12,9	3	3,75	4,207	<0,05
Related bodies (T4)	3	2	2	2,9	1	1,25	0,492	>0,05
Large vessels	3	2	2	2,9	1	1,25	0,492	>0,05

The influence of the characteristics of the tumor according to the T criterion, which is associated with an increase in the prevalence of the primary tumor, on the outcome of the disease was revealed. Adverse prognostic parameters in RCC are the presence of intravascular tumor thrombus and the extent of its prevalence, which affect the staging, treatment, and prognosis of the oncological process. A direct relationship was found between the presence of a tumor thrombus and a decrease in relapse-free and overall survival, as well as an increase in intra- and postoperative complications. At the same time, a worsening prognosis was noted with an increase in the level of lesion of tumor thrombus in venous vessels.

Table 12. The nature and extent of regional metastasis depending on the prognostic group

Parameter	**Total (n=150)**		**Main group (n=70)**		**Control group (n=80)**		**χ2**	**P**
	Абс	**%**	**абс**	**%**	**Абс**	**%**		
Localization of the affected lymph nodes								
at the gate of the kidney regional lymph nodes	4	2,7	1	1,4	3	3,75	0,775	>0,05
along the IVC from the diaphragm to the bifurcation	9	6	7	10	2	2,5	3,874	<0,05
along the aorta from the diaphragm to the bifurcation	4	2,7	3	4,3	1	1,25	1,326	>0,05
enlargement of two or more different groups	3	2	2	2,56	1	1,25	0,492	>0,05
Number of affected groups l / u								
1	19	12,7	13	18,57	6	7,5	4,137	<0,05
2 or more	3	2	2	2,56	1	1,25	0,492	>0,05
N								
N+	22	14,7	15	21,4	7	8,75	4,795	<0,05
N0	128	85,3	55	78,6	73	91,25	4,795	<0,05

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We found that the defeat of the lymph nodes is an indicator of the presence of the metastatic potential of the primary tumor, and also serves as a bad sign that worsens the treatment results and the prognosis of patients ($\chi 2 = 4.795$; $p < 0.05$).The defeat of groups of lymph nodes located along the IVC from the level of the diaphragm to its bifurcation showed a statistically significant adverse effect on the outcome of RCC ($\chi 2 = 3.874$; $p < 0.05$).

One of the most significant characteristics of a tumor is its histological structure. In our study, the most common histological type was clear cell RCC (85.3%), while papillary and chromophobic RCC were much less common (6.6% and 3.3%, respectively). From the prognosis point of view, the aggressive course is characterized by clear-cell RCC, which was more often observed in group I compared with group II, 92.85% and 78.25%, respectively, while chromophobic RCC was found only in the group with a favorable prognosis. Papillary RCC was also characterized by a moderate course of the oncological process; it was more often observed in group II and group I, 11.25% versus 1.43%. Only 1 patient from group I had oncocytic RCC, which was characterized by an extremely unfavorable and highly aggressive course.

Table 13. Important morphological characteristics of tumors and their distribution between prognostic groups

Factors	Total (n=150)	Main group (n=70)		Control group (n=80)		χ2	P
		Абс	%	Абс	%		
TNM classification of primary tumor:							
T1a	24	5	71,4	19	23,75	7.661	<0,01
T1b	36	10	14,3	26	32,5	6,79	<0,01
T2a	38	16	22,9	22	27,5	0,425	>0,05
T2b	9	6	8,6	3	3,75	1,539	>0,05
T3a	27	21	30	6	7,5	12,805	<0,001
T3b	10	8	11,4	2	2,5	4,783	<0,01
T3c	3	2	2,9	1	1,25	0,492	>0,05
T4	3	2	2,9	1	1,25	0,492	>0,05
Histological structure:							
clear cell	128	65	92,85	63	78,75	5,936	<0,05
papillary (chromophilic)	10	1	1,43	9	11,25	5,788	<0,05
Chromophobic	5	0	0	5	6,25	4,526	<0,05
Oncocytic	1	1	1,43	0	0	1,151	>0,05
Sarcomatous	6	3	4,3	3	3,75	0,028	>0,05
Presence of tumor necrosis							
Yes	57	45	64,3	12	15	38,491	<0,001
No	93	25	35,7	68	85	38,491	<0,001
Differentiation degree							
G I	30	12	17,1	18	22,5	0,67	>0,05
G II	52	15	21,5	37	46,2	10,16	<0,01
G III	39	24	34,3	15	18,8	4,68	<0,05
G IV	29	19	27,1	10	12,5	5,133	<0,05
Lymphovascular invasion							
Yes	49	34	48,6	15	18,75	15,09	<0,001
No	101	36	51,4	65	81,25	15,09	<0,001
Infiltration of the tumor with lymphocytes							
Yes	47	29	41,4	18	22,5	6.217	<0,01
No	103	41	58,6	62	77,5	6.217	<0,01
Parenchyma to tumor stroma ratio							
Pronounced stroma	44	15	21,4	29	36,25	3,956	<0,05
Lean stroma	106	55	78,6	51	63,75	3,956	<0,05

Another important histological characteristic of RCC is the degree of tumor differentiation.

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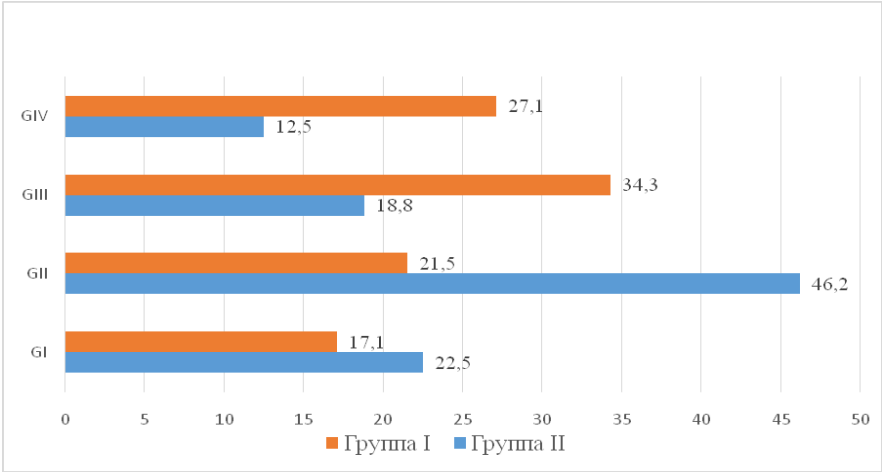

Figure 3. Distribution of the degree of tumor differentiation between the prognostic groups of RCC

Based on the analysis, a correlation was revealed between the degree of differentiation and the outcome of the disease, which may be due to an increase in the virulence of the neoplasm, which is associated with an increase in antigenic simplification, as a rule, found in poorly differentiated forms of RCC. This, in turn, has a stimulating effect on the ability to metastasize. Among patients with low- and undifferentiated tumors, disease progression was more often observed, which served as an unfavorable prognosis factor ($p < 0.05$).

We also studied the prognostic value of the presence of tumor necrosis. As a result of the study and statistical processing of the available material, we found that the presence of tumor necrosis was more often observed in the poor prognosis group compared with the good prognosis group, 64.3% and 15%, respectively, and indicates a rapidly growing and aggressive tumor, which is unfavorable. predictive factor for RCC.

A possible explanation may be a tumor infarction as a result of venous thrombosis, excessive tumor growth and inconsistency with its growth in the development of the vascular network.

According to the studied literature, the role and influence on the prognosis of lymphovascular invasion in RCC are not well understood. LVI is an indicator of invasion of lymphatic and / or blood vessels in the peritumoral area of tumor emboli. Although its mechanism is not clear enough, LVI can reflect the state of the surrounding tumor microenvironment and is a predictor of poor prognosis and aggressive tumor behavior. In this connection, we also studied this parameter, and its possible impact on the outcome.

Based on data analysis, a negative prognostic effect of PVI on the course of RCC was revealed ($\chi 2 = 15.094$; $p < 0.001$). Patients with PVI were more likely to have lesions of regional lymph nodes, the development of locoregional relapses and distant metastases, as well as a decrease in relapse-free and overall survival.

Recently, much attention has been paid to the study of the influence of the microenvironment on the course and outcome of the neoplastic process. Research shows that there are complex interactions between malignant cells and cells in the microenvironment. From the studied literary sources, a small number of studies were revealed to study the role of the ratio of stroma to tumor parenchyma in RCC, as a result of which we analyzed the effect of this parameter on prognosis. Our own observations showed that tumors with a pronounced stroma had a poor prognosis ($\chi 2 = 6.217$; $p < 0.01$), while tumors with a poor stroma had a favorable course and prognosis.

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Thus, a high content of stromal cells in the structure of solid tumors is associated with a poor prognosis, which is possibly associated with the activation of malignant cells by the connective tissue component of the tumor stroma. Along with this, a developing tumor, interacting with the body among other systems, including the immune system, introduces new elements into the nature of these relationships, which in turn are reflected in the biological properties of a growing tumor.

An analysis of the available literature sources showed that most studies are devoted to the study of molecular biological markers and their influence on the prognosis in RCC, when the process is already metastatic, while the role of biomarkers in primary RCC is not well understood. In this regard, we analyzed the prognostic value of some promising biomarkers, such as PD-1, PD-L1, VEGF-A, KIT and mTOR, studied the frequency of expression of these receptors, their effect on disease-free and overall survival, depending on their presence, as well as correlations with other clinical and morphological parameters of RCC and their influence on the course, response to treatment and outcome of the disease.

Table 14 shows significant prognostic parameters and their proportion in the prognosis of the disease.

Table 14. Prognostically significant molecular biological parameters and their factor loading

Parameter	**Total (n=150)**		**Main group (n=70)**		**Control group (n=80)**		**χ2**	**P**
	абс	**%**	**абс**	**%**	**абс**	**%**		
PD-1 will put.	40	26,7	28	40	12	15	11,932	<0,001
PD-1 negative	110	73,3	42	60	68	85	11,932	<0,001
PD-L1 will put.	20	13,3	14	20	6	7,5	5,048	<0.05
PD-L1 negative	130	86,7	56	80	74	92,5	5,048	<0.05
VEGF-A will put	84	56	54	77,1	30	37,5	23,811	<0,001
VEGF-A negative	66	44	16	22,9	50	62,5	23,811	<0,001
mTOR will put.	10	6,7	9	12,9	1	1,25	8,08	<0,01
mTOR neg.	140	9,3	61	87,1	79	98,75	8,08	<0,01
KIT will put.	6	4	1	1,4	5	6,25	2,26	>0,05
KIT neg.	144	96	69	98,6	75	93,75	2,26	>0,05
Proliferation index Ki-67								
Low	114	76	42	60	72	90	18,421	<0,001

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Tall	36	24	28	40	8	10	18,421	<0,001

Analysis of the frequency of expression of real markers among both groups of RCC patients was PD-1 - 26.7%, PD-L1 - 13.5%, VEGF-A - 56%, mTOR - 6.7%, KIT - 2.26%.

A more detailed study of the distribution of the expression of the above biomarkers revealed that in the group of RCC patients with a poor prognosis, the expression of receptors was statistically significantly significantly different compared with the group with a favorable prognosis. The most common marker with high expression in both groups was the VEGF-A marker, which was expressed in groups I and II in 77.1% and 37.5% of cases, respectively. Expression of PD-1 in group I was 40%, while in group II it was only 15%. In group I, a positive PD-L1 status was found in 20% of cases, while in group II, in 7.5% of cases. Expression of mTOR was observed much less frequently, while there was a statistically significant difference in expression in both groups (12.8% and 1.25%, respectively).

The study found that the expression of VEGF-A in patients with RCC correlated with an increased risk of recurrence and metastasis; in addition, there was a decrease in survival ($\chi 2 = 23.811$; $p < 0.001$). The conducted factor analysis made it possible to single out the most prognostically significant parameters for the prognosis of RCC. Using the method of maximum likelihood, an integral prognostic nomogram has been developed, which allows with high accuracy to determine the risk group of a patient with RCC (Table 15).

Table 15. Integral prognostic nomogram for patients with primary RCC after surgical treatment

Factor prognosis	**score (Z)**
Age:	
up to 45 years old	0,6774
45-59 years old	0,07126
60-75 years old	-0,210492
over 75 years old	-0,395896
Symptoms:	
local symptoms	
there is	-0,802581
No	0,57671
general symptoms	
there is	-0,441016
No	2,57452
Changes in blood counts	
Thrombocytosis	
there is	-0,780159
No	0,20875
Anemia	
there is	-0,594347
No	1,92059
Coagulation	
Normocoagulation	-0,429797
Hypo / hypercoagulability	0,36431
Accompanying illnesses	
No	0,59736
Mild severity	0,55962
Moderate severity	-1,189584
Severe degree	-0,895671
T	
T1a	1,20147
T1b	0,82198

T2a	0,18492
T2b	-0,826679
T3a	-1,386294
T3b	-1,519826
T3c	-0,826679
T4	-0,826679
N	
N+	-0,14959
N0	0,895671
The presence of a tumor thrombus	
there is	-1,232144
No	0,36795
Histological structure	
Clear cell	-0,164784
Papillary	2,06369
Chromophobic	0
Oncocytic	0
With sarcomatous component	-0,133531
Differentiation degree	
GI-GII	0,57796
GIII-GIV	-0,675856
Presence of necrosis	
Yes	-1,455287
No	0,8671
Lymphovascular invasion	
Yes	-0,951842
No	0,45734
Ratio of stroma to tumor parenchyma	
Lean stroma	0,52571
Pronounced stroma	-0,209039
Infiltration of the tumor with lymphocytes	
Yes	-0,610455
No	0,28003
Expression of receptors	
PD-1	
Positive	-0,980829
Negative	0,34831
PD-L1	
Positive	-0,980829
Negative	0,14518
VEGF-A	
Positive	-0,721318
Negative	1,0059
mTOR	
Positive	-2,330756
Negative	0,12504
KIT	
Positive	0,08961
Negative	-0,380391
Level ki-67	
Low	0,40547
Tall	-1,386294

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Operation volume	
Kidney resection	-0,23419
Radical nephrectomy	1,098612
Radical nephradrenalectomy	0,42608
Lymph node dissection volume	
Optional	0,81093
Selective	-1,232144
Extended	0,67209
Not carried out	-1,126783
Blood loss	
Up to 200 ml	0,8473
200-400 ml	0,05368
More than 400 ml	-0,721318
Duration of surgical treatment	
Up to 1.5 hours	1,32687
More than 1.5 hours	-0,998529
Wound healing	
Primary	0,456
Secondary	-1,519826
Low risk + 8.5- + 18.0	
Average risk -10.7- + 8.4	
High risk -23.1 -10.8	

The difference between this nomogram is that it included clinical and morphological, as well as molecular biological parameters that were not included in the prognostic scales and models existing today. According to the total score, patients can be divided into risk groups for the development of relapses and metastases: a high-risk group with a total score of -23.1 to -10.8, an average risk from -10.7 to +8.4 and a low risk of +8.5 to -18.0.

Table 16. Algorithm for managing patients with primary RCC in the postoperative period depending on the risk group

Stage of the disease	**Surgical tactics**	**Risk degree**	**Management tactics**
Stage I, II, III	Radical resection / nephrectomy	Low to medium risk	Observation
			• Expression of angiogenesis factors (VEGF-A, KIT):angiogenesis inhibitors • Expression of PD-1, PD-L1: • PD-1 / PD-L1 inhibitors • Expression of mTOR: • mTOR inhibitors • In case of negative receptor status or impossibility of IHC or targeted therapy: • immunotherapy with interleukins or interferon
StageIV	Nephrectomy / combined surgery		

In patients with a high risk of relapse and metastases, more intensive follow-up and adjuvant immuno- and targeted therapy should be carried out, depending on the type of expressed markers.
The criteria for conducting adjuvant therapy are:

- T3, T4;
- The size of the tumor is more than 10 cm;
- Damage to the lymph nodes;
- Presence of a tumor thrombus;

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- Clear cell RCC with histological characteristics such as low differentiation (GIII-GIV), presence of necrosis, lymphovascular invasion, pronounced tumor stroma, absence of lymphocyte infiltration;
- Oncocytic, sarcomatous RCC
- Expression of receptors (VEGF-A, mTOR, PD-1, PD-L1);
- High proliferation index

Table 17. Algorithm of dynamic observation depending on the stage of the disease

		First 3 years	3-5 years	More than 5 years
Stage I	Abdominal cavity	Preferably MSCT / MRI or ultrasound for 3-12 months 1 time per year	Annually as clinically indicated	According to clinical indications
	Thorax	Annually chest x-ray or CT	Annually chest x-ray or CT	According to clinical indications
Stage II or III	Abdominal cavity	Preferably MSCT / MRI or ultrasound within 3 months in 1 year, next 2 years 6 months	Preferably MSCT / MRI or ultrasound for 3-12 months 1 time per year	According to clinical indications
	Thorax	Annually chest x-ray or CT for 3 months in 1 year, next 2 years 6 months	Annually chest x-ray or CT	According to clinical indications

The follow-up algorithm is a modified table of the American Association for Urology Teaching and Research.

Table 18. Dynamic observation algorithm depending on the risk category

Follow-up studies	Radical resection or nephrectomy	
Objective examination	Questioning and physical examination aimed at identifying symptoms and signs to detect relapse or distant metastases	
Laboratory research	Biochemical blood test (urea, creatinine, uric acid, LDH, alkaline phosphatase, calcium level)	
Skeletal bone scan	General blood analysis	
Examination of the brain	Coagulogram	
	Low risk	**Medium to high risk**
Abdominal examination	CT or MRI every 3 months during the year, then if there are no changes according to the radiation methods, then once a year	CT or MRI every 3-6 months for a year, then every 6 months for 3 years, then once a year for up to 5 years
Chest examination	Chest x-ray once a year for 3 years, after 3 years if symptoms appear	Using research when symptoms appear

Conclusions

Clinical, laboratory and morphological parameters can have both favorable and unfavorable statistically significant effects on the prognosis of RCC. Senile age, the presence of severe concomitant pathology, changes in blood parameters: thrombocytosis, anemia, hemostasis disorders negatively affect the outcome of RCC ($p < 0.05 - 0.001$).Biological characteristics of the tumor as: low degree of differentiation (GIII-GIV), the presence of tumor necrosis, LVI, pronounced tumor stroma ($p < 0.05 - 0.001$) are unfavorable, while a high degree of differentiation (GI-GII), absence tumor necrosis, LVI, scant stroma, tumor infiltration with lymphocytes are favorable factors for the prognosis of RCC ($p < 0.05 - 0.001$).The frequency of marker expression among RCC patients was PD-1 - 26.7%, PD-L1 - 13.5%, VEGF-A-56%, mTOR-6.7%, KIT-2.26%, while their expression negatively affects the prognosis of

the disease (p <0.05 - 0.001).The use of immuno- and targeted therapy in RCC patients with a high risk category for recurrence and / or metastases leads to improved long-term results of treatment $\chi 2 = 4.2$; p <0.05 and $\chi 2 = 11.336$; p <0.001, respectively).The developed algorithm for managing patients based on the prognostic nomogram allows improving treatment rates, while the dynamic observation algorithm makes it possible to timely diagnose the development of relapses and metastases of RCC.

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