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SEMENOV

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PERSONALIZATION OF COMPLENX TREATMENT BASED ON CLINICAL AND MORPHOLOGICAL PROGNOSTIC FACTORS IN PATIENTS WITH METASTATIC RENAL CANCER

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DISCUSSION
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INTRODUCTION

Relevance of the research topic

Renal cell cancer (RCC) in modern oncourology is a malignant disease with increasing morbidity and mortality rates worldwide, as well as an increasing incidence of metastatic forms detected for the first time [81, 231, 273]. At primary diagnosis, renal cell cancer metastases are detected in 20-30% of patients, and in another 20-50% they appear during the progression of the tumor process at various times after surgical treatment [9, 23, 60]. Metastatic foci or dissemination of the tumor process are more often found in the lungs (55%), lymph nodes (34%), bones (32%), liver (32%), adrenal glands (19%), contralateral kidney (11%), and brain (5.7%) [5, 6, 8, 16, 17,19, 26, 28, 58, 88, 133, 134, 150, 239, 251, 263].

Analysis of the literature has shown that the survival rates of mRCC patients are disappointing; the median overall survival (OS) averaged 4 to 20 months, and the expected 5-year survival rate was <20% [123, 180]. Until recently, mRCC was considered a disease with a poor prognosis [155, 281], and during the "cytokine era" the range of indications for palliative nephrectomy [79, 213] and radiation therapy for symptomatic purposes [146, 235] has expanded.

Over the past 20 years, there have been some advances in the treatment of mRCC due to the introduction of tyrosine kinase inhibitors (TKI) into systemic antitumor therapy [7, 12,14, 20, 45, 52, 74, 109, 120, 183, 185, 218, 222, 248, 253].

Currently, the paradigm of mRCC treatment has changed over the last decade from cytokine immunotherapy, targeted therapy to treatment with checkpoint inhibitors (ICI) and their combinations with other antitumor drugs [194]. According to clinical trials, targeting drugs have demonstrated high efficacy, improved overall and recurrence-free survival, safety and good tolerability in the treatment of mRCC [44, 112, 184]. The choice of targeted therapy is based on the use of the IMDC prognostic model [32]. Due to the introduction of modern immunoncologic drugs into

clinical practice, ICI and their use in combination with TKI have significantly improved the results of drug treatment, which led to an increase in survival rates of mRCC patients [122, 164, 178, 268]. However, there are currently no criteria for the selection of immunoncologic agents. In this regard, it is highly relevant to revise the existing prognostic scales in terms of the heterogeneity of mRCC, whose survival rates are influenced by the nature and number of metastases, histological subtype and degree of tumor differentiation.

The use of modern drug therapy has made it possible to more actively use palliative surgical approaches in the treatment of mRCC – palliative nephrectomy, removal of solitary metastases, which also increases the possibility of disease control with an increase in survival rates [3, 10, 15, 18, 172, 173, 234]. However, as experience is accumulated in real clinical practice, palliative surgeries are not justified in all cases. Therefore, it is necessary to identify a group of patients with unfavorable prognosis who would benefit from cytoreductive surgery.

Degree of development of the research topic

In recent years, there has been a progressive increase in the number of publications devoted to the study of complex treatment based on clinical and morphologic prognostic factors in patients with metastatic renal cancer.

However, despite the progress achieved so far, there are no prospective clinical studies comparing clinical and laboratory, pathomorphological characteristics of the tumor, the number of affected organs, the time of occurrence and localization of metastases. There are no clear representations of the use of ICI taking into account clinical, laboratory and pathomorphologic parameters and their impact on overall survival and progression-free survival. The developed personalized survival models for mRCC patients are not perfect. To date, the personalized approach is applied only by IMDC prognosis groups to improve survival and quality of life, but currently it is not enough, because there is no data on the presence of visceral crisis, clinical, laboratory and pathomorphological parameters of patients are not taken into account.

mRCC is a heterogeneous disease, the course and prognosis of which is influenced by a large number of factors, from the general medical status of the patient (ECOG) to the histological subtype of the tumor. In this regard, it is necessary to expand the panel of factors for more personalized approach in antitumor treatment of mRCC taking into account such indicators of metastatic process as histological variants, tumor differentiation degree, number of affected organs, time of occurrence and localization of metastases, as well as laboratory data. It is important to determine the prognosis group of mRCC patients who will have an advantage in survival rates during cytoreductive surgical interventions.

Thus, the systematization and generalization of the currently available comprehensive data of personalized approach to the treatment of mRCC is an urgent problem of modern oncourology.

All this explains the necessity and relevance of performing this dissertation work.

Purpose of the study

Study of clinical and morphological features of mRCC to form prognostic groups to determine the personalized choice of antitumor drug treatment and cytoreductive surgical interventions to increase survival rates.

Research Objectives

1. To study the influence of the results of clinical and laboratory tests, pathomorphological characteristics of the tumor, localization and number of metastases, time of their occurrence on the survival rates of mRCC patients. To add statistically significant prognostic factors for a personalized approach to mRCC treatment.
2. To study the impact of cytoreductive surgeries on survival rates in mRCC patients taking into account extended clinical and morphologic prognostic factors.
3. To analyze the efficacy of systemic therapy in patients with mRCC taking into account the evaluation of clinical and morphological prognostic factors.

4. To create a mathematical model for predicting the 5-year survival rates of patients with mRCC and evaluate using ROC analysis.

5. To create a multifactorial mathematical model for predicting 10-year survival of patients with mRCC based on the most significant predictors.

6. To create a personalized prognosis model for mRCC patients based on 8 independent statistically significant prognostic factors (type and number of metastases, degree of tumor differentiation according to Fuhrman, hemoglobin level, ECOG status, cytoreductive nephrectomy (CN) and metastasectomy, presence or absence of visceral metastases).

7. To study in a modified SOSh model subgroups of unfavorable and very unfavorable prognosis predictive factors and their influence on survival rates in mRCC patients.

8. To evaluate the impact of cytoreductive surgery on survival rates using a modified SOSh model in mRCC patients with unfavorable and very unfavorable prognosis.

9. To study the efficacy of first and second line systemic therapy in patients with mRCC of unfavorable and very unfavorable prognosis in the modified SOSh model and compare with IMDC prognosis groups.

Practical significance of the study

The application of a personalized modified SOSh model for predicting the survival rates of patients taking into account the identified additional prognostic factors was substantiated. This mathematical model can be used in practical healthcare to optimize the treatment of patients with mRCC. CN is indicated for patients in the subgroup of unfavorable prognosis according to SOSh.

Material and methods of research

The study is retrospective and included 981 patients with metastatic renal cell cancer who received systemic therapy at the Municipal Oncologic Hospital No. 62 in

Moscow and the Municipal Oncologic Dispensary in St. Petersburg from 2006 to 2022. Of the 981 patients, 877 patients received only targeted therapy, and 94 patients received immunotherapy with immune checkpoint inhibitors in addition to targeted therapy. When analyzing the frequency of objective effects, time to progression, survival rates, and factors affecting these parameters, we combined all 981 patients into a single group because all patients received different variants of systemic therapy.

The following methods were used in the conduct of the study:

1. Working with archival material.
2. Filling in the databases.
3. Questionnaire and survey of patients, collection of information on survival rates and long-term results of complex therapy of mRCC patients.
4. Standard methods of laboratory and instrumental diagnostics (general, biochemical blood tests, CT scan of thoracic and abdominal organs, MRI of the small pelvis, bone scan).
5. Statistical processing of the data.

Scientific novelty of the study

In the dissertation work:

For the first time, as a result of a retrospective clinical study in the Russian Federation, the analysis was performed and the dependence of clinical and laboratory parameters, pathomorphological characteristics of the tumor, the number of affected organs, the time of occurrence and localization of metastases on survival rates of mRCC patients was established.

For the first time, the impact of additional prognostic factors on survival rates and objective response rates and time without progression in mRCC patients were evaluated in single- and multivariate analyses.

The necessity of using such characteristics as the degree of differentiation and histological variants of the tumor and laboratory data, which have a significant

impact on the features of the metastatic process and should be taken into account in the approach to the prescription of systemic therapy, has been convincingly proved.

Groups with different recurrence-free periods in mRCC patients were studied and prognostic factors affecting survival rates were evaluated.

In the conducted study we studied prognostic factors influencing survival rates in patients with mRCC depending on the type and number of metastases.

In real clinical practice, the factors influencing the survival rates of mRCC patients during cytoreductive surgeries have been studied and established. The main factors that had a statistically significant impact on the outcome and survival rates of mRCC patients were the degree of tumor differentiation according to Fuhrman, the number of metastases, as well as metastases to the liver and brain. The study revealed that the IMDC model is currently insufficient for selecting patients with mRCC for cytoreductive surgery.

The efficacy of systemic therapy for mRCC patients was analyzed taking into account the evaluation of clinical and morphological prognostic factors influencing survival rates. It was proved that immuno-oncologic drugs (nivolumab, ipilimumab, atezolizumab and pembrolizumab) should be used in patients with single and multiple metastases of mRCC.

A logistic regression model for predicting the 5-year OS of patients was created and evaluated using ROC analysis.

In this study, we performed Cox multivariate analysis to identify statistically significant prognostic factors affecting survival rates in 981 mRCC patients. We identified and examined 8 significant prognostic factors, including type and number of metastases, Fuhrman tumor differentiation grade, hemoglobin level, ECOG status, CN and metastasectomy, and presence or absence of visceral metastases. For the first time in a retrospective study, we created a modified model (SOSh) taking into account personalized prognostic factors and implemented a scoring system to evaluate the prognosis of survival rates of patients with mRCC depending on 8 independent prognostic factors. The use of this model may lead to an increase in the efficacy of personalized systemic therapy and survival rates in patients with mRCC.

For the first time, according to the SOSh prognostic model, the third and fourth subgroups of unfavorable and very unfavorable prognosis in mRCC patients were singled out. In the groups of unfavorable and very unfavorable prognosis in mRCC patients the prognostic factors and their influence on survival rates in mRCC patients were studied. In single- and multivariate analysis the degree of tumor differentiation, number of metastases, ECOG status, hemoglobin level and performance of CN were additional factors influencing the survival rates in mRCC patients. This division of unfavorable prognosis group is necessary for more effective approach to personalized systemic therapy in mRCC patients. In real clinical practice the influence of cytoreductive surgeries on survival rates using the modified SOSh model in mRCC patients with unfavorable and very unfavorable prognosis was estimated. It was studied and proved that CN is indicated for mRCC patients of the subgroup of unfavorable prognosis according to SOSh. It has been found that patients given immunotherapy and combinations in the first and second line obtained a difference in treatment response in patients with intermediate and unfavorable prognosis according to SOSh mRCC.

Theoretical and practical significance of the work

We studied and obtained new data on the influence of clinical and laboratory parameters and pathomorphological characteristics of the tumor, the number of affected organs, the time of occurrence and localization of metastases on the survival rates of mRCC patients. The 4 group of very unfavorable prognosis was singled out and prognostic factors and their influence on survival rates in mRCC patients were studied.

The modern strategy of complex treatment of mRCC is formulated. The application of a personalized model for predicting the survival rate of patients taking into account the identified additional prognostic factors is substantiated. The necessity of additional prognostic factors allocation for increasing the effectiveness of systemic therapy is established. This mathematical model can be used in practical healthcare.

The use of immuno-oncologic drugs is reasonable in single and multiple metastases of RCC. It is necessary to use combination therapy with inclusion of immuno-oncologic drugs in the first line in patients with single and multiple metastases of RCC. On the basis of our modified model in the group of unfavorable prognosis, despite the inclusion of additional prognostic factors, combinations of modern systemic drugs should be used. And in the group of favorable prognosis it is possible to carry out less intensive treatment in monotherapy mode.

Implementation of the study results in the practice of health care

The application of personalized prognosis model in patients with mRCC is implemented in the clinical practice of work in the department of oncourology and clinical oncology of St. Petersburg State Budgetary Institution "City Clinical Oncological Dispensary" and Moscow City Oncological Hospital № 62.

The analyzed efficacy of systemic therapy in patients with mRCC taking into account the evaluation of clinical and morphological prognostic factors, which has found active application in the oncourology department of St. Petersburg GBUZ "City Clinical Oncological Dispensary" and GBUZ Moscow City Oncological Hospital № 62, has found its justification both in theory (based on the results) and in everyday clinical practice.

Materials of the dissertation are used in the educational process of the Oncology Department of St. Petersburg State University (act of implementation from 2024).

Methodology and methods of the dissertation research

The thesis work was carried out in a comparative study design using general clinical, anamnestic, laboratory and statistical methods of investigation.

Main scientific results

Publications

1. The heterogeneity of the intermediate prediction group is revealed [2]. Pp. 121, 150. A statistically significant difference in 5-year OS was determined in mRCC patients with 1 or 2 unfavorable additional prognostic factors, with median survival rates of 52 and 34 months, respectively ($p<0.0001$). Author's contribution is 100%.

2. 2 We studied the effect of systemic therapy on survival rates in patients with mRCC [12]. Pp. 11, 69.

3. A group of patients with solitary bone metastases was studied [16, 17, 19]. Pp. 11, 38, 163. A design patent was obtained - “Scheme - algorithm for the treatment of solitary kidney cancer metastases in bone”. No. 111898 dated 04.05.2018 Author's contribution 25%.

4. A group of patients with single metastases to bone was studied [6]. Pp. 178. A design patent was obtained - “Scheme - algorithm for the treatment of single kidney cancer metastases in bone” No. 113723 dated 19.10.2018. Author's contribution 25%.

5. The effect of cytoreductive surgeries on survival rates in patients with solitary metastases of RCC was studied [10]. Pp. 12, 231, 242.

6. The difference in OS rates in mRCC patients depending on the performance of CN has been studied and proven [15, 18]. Pp. 12, 231, 278, 336. The median 5-year OS was 36 months in patients who underwent CN and 11 months in patients who did not undergo CN ($p<0.0001$).

7. On the basis of the studied additional clinical and morphological parameters we developed “Scheme-algorithm model for predicting the survival rate of mRCC patients” № 134774 dated 21.09.2023 Page. 376. Author's contribution is 50%.

8. We analyzed cytoreductive surgeries on survival rates in patients with oligometastatic renal cancer [3]. Pp. 12.

9. A modified personalized prognosis model for mRCC patients SOSh was developed (Semenov, Orlova, Shirokorad). Pp. 383-408. For the first time, according

to the SOSh prognostic model the fourth additional group of very unfavorable prognosis in mPCR patients was singled out. The median OS in the subgroup of unfavorable and very unfavorable prognosis according to SOSh was 29.5 and 12.3 months, respectively (p<0,0001). Author's contribution 100%.

10. It was found that CN is indicated in the SOSh unfavorable prognosis group (p=0.02) and inappropriate in very poor prognosis patients (p=0.28). Pages. 409-410. Author's contribution 100%.

11. It has been shown that when 2nd line systemic therapy is administered to mRCC patients in IMDC and modified SOSh prognosis groups, there is a difference in response in patients with unfavorable prognosis according to SOSh with targeted therapy (p=0.014 and p=0.003); when using immunotherapy in first and second line intermediate (p=0.032 and p=0.011), (p=0.039 and p=0.017) and unfavorable prognosis according to SOSh (p=0.037 and p=0.0079), (p=0.042 and p=0.042). Pp. 413-420. Author Contribution 100%.

Degree of reliability of the results of the work and their approbation

The author analyzed foreign and domestic literature sources devoted to the study of current prognostic factors in patients with metastatic renal cell cancer. The author developed the design of the study. The work with the analysis of the obtained results of the study, their interpretation, as well as the performance of statistical processing of data was carried out by the author personally. The author analyzed the efficacy of systemic therapy in patients with mRCC taking into account the evaluation of clinical and morphological prognostic factors and developed a model for prediction of 5-year OS indicators of mRCC patients. He also developed and implemented the proposed personalized SOSh model based on independent statistically significant additional prognostic factors.

The results of the research and the main provisions of the work were reported and discussed at the IV Nevsky Urological Forum (Russia, St. Petersburg, June 7-8, 2018); V Nevsky Urological Forum (Russia, St. Petersburg, June 2-3, 2022);

conference "Three pillars of clinical oncology: how do you treat?" (Russia, St. Petersburg, April 6-7, 2023); XI Congress of Urologists of Siberia" (Russia, Krasnoyarsk, May 19-20, 2023); First Eurasian Forum on Oncourology, Kazakhstan (Astana, May 26, 2023); VII Polessky Urological Forum (Belarus, Gomel, June 8-9, 2023); VI International Forum on Oncology and Radiotherapy (Russia, Moscow, September 13, 2023); Interdisciplinary scientific-practical conference with international participation "Endourocenter meeting – 2023; VII scientific-practical conference of urologists of the North-West Federal District on April 13, 2024; Second Eurasian Forum on Oncourology (Uzbekistan, Samarkand, April 19, 2024).

The author within the framework of the thesis work obtained three patents related to the diagnosis and treatment of mRCC patients: No. 134774 dated 21.09.2023 "Scheme-Algorithm of the model for predicting the survival rate of mRCC patients"; No. 111898 dated 04.05.2018. "Scheme-Algorithm for treatment of solitary kidney cancer metastases to bone"; No. 113723 dated 19.10.2018. "Scheme-Algorithm for treatment of solitary metastases of renal cancer in bone".

Publications

On the topic of the dissertation published: 18 printed works, 18 of them in the journal recommended by the VAK of the Ministry of Education of the Russian Federation for publication of the main results of dissertations for the degree of Doctor of Medical Sciences. 3 patents of the Russian Federation for industrial design were obtained.

The results of the conducted work were accepted as publications in the form of posters within the framework of the RUSSCO 2023 conference (2 posters).

Structure and scope of the thesis

The thesis is presented on 454 pages of typewritten text and consists of an introduction, literature review, description of materials and methods of research,

results of own research and their discussion, conclusions, practical recommendations and a list of literature, including 21 domestic and 261 foreign sources. The work is illustrated with 207 tables and 166 figures.

Provisions for defense

1. Clinical and laboratory parameters and pathomorphological characteristics of the tumor, the number of affected organs, the time of occurrence and localization of metastases influenced the survival rates of mRCC patients. Statistically significant prognostic factors for a personalized approach to mRCC treatment were added.

2. The effect of cytoreductive nephrectomy on survival rates with regard to extended clinical and morphologic prognostic factors in mRCC patients was studied.

3. The efficacy of systemic therapy in patients with mRCC was analyzed taking into account the evaluation of clinical and morphological prognostic factors.

4. A mathematical model for predicting the 5-year survival rates of mRCC patients was created and evaluated using ROC analysis.

5. A multifactorial mathematical model for predicting 10-year survival of mRCC patients based on the most significant predictors was created.

6. A personalized prognosis model for mRCC patients was created based on 8 independent statistically significant prognostic factors (type and number of metastases, tumor differentiation degree according to Fuhrman, hemoglobin level, ECOG status, CN and metastasectomy, presence or absence of visceral metastases).

7. Predictive factors and their influence on survival rates in mRCC patients of the unfavorable prognosis group in the modified SOSh model were studied.

8. The impact of cytoreductive surgery on survival rates using the modified SOSh model in mRCC patients with unfavorable and very unfavorable prognosis was evaluated.

9. We studied the efficacy of first and second line systemic therapy in patients with mRCC of unfavorable and very unfavorable prognosis in a modified SOSh model.

Chapter 1
METASTATIC KIDNEY CANCER: CLINICAL AND MORPHOLOGICAL FEATURES AND THE CURRENT FEATURES OF CLINICAL TACTICS AND PROGNOSIS (LITERATURE REVIEW)

1.1 Morbidity and mortality rates for metastatic renal cell cancer

Improvement of medical care and socio-economic indicators leads to an increase in life expectancy of the population and, as a consequence, entails an increase in the incidence of malignant neoplasms. RCC is one of the most common malignant tumors of the genitourinary system, accounting for 3% of the percentage of all malignant neoplasms in adults worldwide [98]. The incidence has increased by approximately 2% each year over the past two decades [99]. One-third of patients with initially diagnosed RCC are found to have distant metastases, which severely affect patients' quality of life and significantly reduce survival [108]. In the RENSUR3 study, the median survival time for mRCC patients in the entire cohort was 11.9 months [180].

Given the poor prognosis of mRCC patients, the medical community is now placing more emphasis on clinical prognostic assessment and personalized therapy for patients [69].

Continued advances in imaging technology and frequent medical examinations have contributed to a higher detection rate of mRCC [126], and 16% of patients who seek medical care have already been found to have distant metastases [144]. Approximately 35% of patients with mRCC, even after radical nephrectomy or renal resection, later developed metastases or recurrence. Until recently, mRCC was difficult to treat, with a 5-year survival rate of only 12% [97]. The lack of validated biomarkers and insufficient knowledge of the biological processes occurring during the progression of mRCC were the main reasons for the ineffectiveness of therapy [102].

However, the search for new treatment methods and the widespread use of targeted drugs allowed to significantly affect the duration of OS. Thus the median OS was 12 months in patients who started first-line systemic therapy between 2000 and 2005, already 15 months between 2006 and 2011, 24 months between 2012 and 2017, and not reached in those who started treatment between 2018 and 2020. The 2-year ORs were 23%, 34%, 50%, and 59%, respectively; the 5-year OS in the first 3 grapes were 7%, 14%, and 24%, respectively [179].

In recent years, the clinical application of novel vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKI) and ICI has led to significant progress in the treatment of mRCC. Adverse events of therapy remained a problematic area requiring improvement and selection of appropriate treatment for various forms of metastasis [227].

Thus, knowledge of prognosis and clinicopathologic features will help in making the most optimal clinical decisions for each individual patient. Given the poor prognosis of patients with mRCC, new predictors for predicting patient response to therapy are being actively sought. In this context, researchers are actively engaged in the construction of nomograms for OS and progression-free survival (PFS) of patients with mRCC [84, 282], which can help clinicians to predict survival time and choose optimal treatment strategies, which is the most important problem of modern oncourology. The literature has analyzed the influence of certain constitutional, clinical-morphologic, and laboratory factors on survival rates, which are either already included in prognostic models or considered as potential prognostic factors [40, 119, 160].

1.2 Clinical and laboratory parameters in patients with metastatic cancer renal cell carcinoma and their prognostic value

mRCC is characterized by a variety of clinical manifestations, ranging from an asymptomatic course with a long life expectancy to a violent course with a poor

prognosis despite treatment [271]. Over the years, clinical and laboratory characteristics reflecting tumor biology have been found to correlate with patient survival. It was found that laboratory parameters strongly influenced prognosis. And based on these indicators, several prognostic models (MSKCC and (IMDC)) have been developed successively [138, 195]. According to the literature, risk factors for mRCC are age, sex, race, T and N status, histologic type, ECOG status, previous nephrectomy, number of previous courses of systemic therapy, IMDC risk groups, and number of metastatic foci [160]. Among all risk factors, age, gender, and race can be prognostic factors for mRCC. Patients older than 70 years of age had a better OR compared with patients younger than 70 years of age (OR, 0.65; 95% CI, 0.48-0.89); however, there was no significant difference in PFS between the two groups (OR 0.73; 95% CI 0.51-1.06) [160]. Males had worse OS than females (OR 1.48; 95% CI 1.14-1.93); however, there was no significant difference in PFS between the two groups (OR 1.10; 95% CI 0.85-1.44) [160].

In a special review of multivariate survival analysis of patients with four metastases, pT and pN stage predicted a worse prognosis for mRCC patients [262]. In multivariate analysis, pT and pN stage were independent factors for cancer-specific survival in mRCC. The combination of clinical and molecular markers achieved the best prognostic accuracy [276]. In another study, Tosco et al. [242] determined the role of baseline clinical factors in patients with mRCC who had undergone nephrectomy and at least one metastasectomy [242]. The author proved that pT stage ≥3 and Fuhrman grading degree ≥3 separately lead to a 2.3 – to 2.8-fold increased risk of cancer death. A model based solely on clinical factors (including pT stage and Fuhrman grading) was effective [area under the curve (AUC) at 5 years =0.88]. Other authors did not find any influential role of pT stage or Fuhrman grading, but found a good prognostic role of sarcomatoid changes, which was also confirmed by other reports [32, 161]. In another study, pT stage was a significant risk factor for the prognosis of patients [53]. The grading of pT3 and pT4 are significantly associated with unfavorable prognosis [168]. In addition, patients with pT3 and adrenal invasion

have a significantly worse prognosis [216]. A multivariate Cox regression model showed that pN stage is inversely related to patient prognosis [216].

A primary tumor with a higher ratio of maximal to minimal tumor diameter was an independent prognostic factor for both PFS and OS in patients with a clear cell variant with mRCC in patients receiving targeted therapy. Higher values of this ratio were also associated with high stage pT, sarcomatoid type, presence of tumor necrosis, poor prognosis by MSKCC and IMDC [210]. Tumor size was also used as a prognostic factor in another study. Calculated using a three-dimensional conformal radiotherapy planning system, larger tumor volume together with a higher Fuhrman score, high pT index were associated with shorter OS and cancer-specific survival (CSS), no metastasis, and no local recurrence [272].

Given the increasing incidence of mRCC, scientists' efforts are focused on exploring new prognostic biomarkers that could radically change the way mRCC is diagnosed and treated. Although some of the current research is in its infancy and it is not yet known which biomarkers will become clinically available, many candidate biomarkers are promising and require external validation. Ultimately, biomarkers may allow cost-effective screening and identification of patients with poor prognosis, identification of aggressive cancers among small renal neoplasms, detection of recurrence after surgery with minimal imaging, and the ability to select appropriate systemic therapy for patients with mRCC [162].

For greatest cost-effectiveness, much attention has been given to those biomarkers that are available in routine practice and do not require high-tech expensive techniques. K. Velaer et al. applied a laboratory-wide association study (LWAS) systematic evaluation of common clinical laboratory findings associated with survival in patients diagnosed with mRCC and determined that 14 laboratory tests out of 53 examined were associated with OS. This approach confirmed the association of laboratory parameters currently used in prognostic models with survival, including calcium levels, white blood cell count, platelet count, and hemoglobin, as well as acute phase reagents not typically included in prognostic models, such as serum albumin, ferritin, and alkaline phosphatase [61].

Given the proven prognostic significance of the parameters of the general blood count, many researchers have paid attention to their ratios. Thus, an increase in the ratio of neutrophils to lymphocytes before the start of therapy was associated with low TIA. During treatment, a decrease in the neutrophil-to-lymphocyte ratio was associated with a significant increase in the OS compared to patients with increasing ratios [160]. A lower baseline neutrophil to eosinophil ratio was associated with a better response to mRCC ICI treatment [254]. It was also shown that neutrophil to eosinophil ratio was significantly associated with the frequency of objective response, occurrence of immune-related adverse events, and tumor histologic type, as patients with high ratios were more likely to have non-small cell variants of mRCC in contrast to patients with low ratios [200]. In patients with mRCC treated with sunitinib, a lymphocyte-to-monocyte ratio (>3) and a high platelet-to-lymphocyte ratio (>150) were associated with shorter PFS [204]. Both a high neutrophil-to-platelet ratio and a high combined platelet count and neutrophil-to-lymphocyte ratio were associated with worsened OS in a cohort of mRCC patients receiving pazopanib or sunitinib in the first-line setting [209].

In multivariate analysis, elevated serum glutamyltransferase (GGT) levels were an independent unfavorable prognostic factor along with high neutrophil counts, low albumin, high LDH levels, and high De Ritis coefficient in patients with mRCC on ICI therapy [128]. The duration of first-line PFS, Fuhrman differentiation grade, LDH and albumin levels, corrected calcium levels, and MSKCC and IMDC scores calculated at the beginning of second-line therapy are prognostic factors for patients before starting second-line TKI treatment of clear cell mRCC after progression on the background of ICI [198].

The inflammatory response has been associated with many processes from initiation and development to progression and metastasis in various malignancies, including RCC. Paraneoplastic syndrome with inflammatory response has been frequently demonstrated in patients with advanced RCC [206]. It has been reported that some molecules involved in the inflammatory response such as IL-6 and nuclear factor-kappa β were factors associated with the progression of RCC. The number

of parameters associated with inflammatory response increased in IMDC scale criteria compared to MSKCC. The early decline in serum C-reactive protein (CRP), neutrophil levels, and neutrophil-lymphocyte ratio in patients with mRCC treated with pazopanib during the first month was significantly associated with disease control, suggesting a prognostic role for the first radiologic control [139].

Elevated CRP levels were significantly associated with worse ОЫ in patients receiving ICI. The predicted 2-year OS for patients with CRP values of 0.5, 5, 40, and 150 mg/L was 96%, 73%, 42%, and 23%, respectively, which identified CRP as a powerful prognostic predictor of survival, and its predictive value was superior to the IMDC model [73]. Elevated baseline levels of CRP and neutrophil-to-lymphocyte ratio were factors associated with poor OS and PFS in patients receiving nivolumab for mRCC, and inclusion of baseline CRP levels in the IMDC prognostic model improved its discriminatory ability to predict the duration of OS and PFS from the time of nivolumab initiation [71]. In the group of patients with an overall response to nivolumab therapy, a significant decrease in CRP levels compared to baseline was observed, whereas a significant increase was observed in the group that did not respond to treatment. Even patients with high baseline CRP levels (≥1.5 mg/dL) showed good PFS results if CRP decreased (<1.5 mg/dL) 1 month after treatment [72].

Recent retrospective analyses of large phase II and III studies showed that elevated baseline serum IL-8 levels correlated with higher levels of tumorigenic and circulating immunosuppressive myeloid cells, decreased T-cell activation, and poor response to treatment. These results need to be confirmed in prospective clinical trials; however, they provided evidence for the potential use of serum IL-8 as a biomarker of resistance to VEGFR-ITC and ICI [121].

There is a modified Glasgow prognostic score (mGPS), which was calculated based on serum albumin levels and CRP levels. A baseline mGPS of 2 is associated with a shorter OS and PFS compared with a score of 0. The corresponding median OS of patients with baseline mGPS values of 0, 1, and 2 was 44.5, 15.3, and 10 months, respectively. The median PFS of these three cohorts was 6.7, 4.2, and 2.6 months, respectively [151].

By analyzing data on clear cell RCC from The Cancer Genome Atlas (TCGA), Oncomine and Gene Expression Omnibus (GEO) it was observed that C-chemokines were significantly elevated in tumor tissues and associated with disease progression. Patients with higher levels of C-chemokines had significantly lower OS, PFS and CSS, and a positive correlation was found between C-chemokines and infiltration of 25 immune cell subtypes, many of which affected the prognosis of clear cell RCC, contributing to the prediction of survival and response to immunotherapy, as well as the development of new therapeutic targets for this histologic variant [49].

Immunohistochemical evaluation of programmed death-1 (PD-1) receptors and their ligands (PD-L1) has been used to evaluate advanced malignancies with potential response to ICI. Blockade of immune checkpoint PD-1 and its ligand PD-L1 has been applied in advanced lung, kidney and bladder carcinomas as well as melanoma with promising results in several studies [39]. For clear cell RCC, immunohistochemical evaluation has been selectively performed for intratumoral lymphoid inflammatory infiltrates. However, selection of patients for this form of therapy has been difficult because this evaluation is subject to inter-object variability [22]. In fact, up to 17% of patients with negative immunohistochemistry results did respond to ICI [143]. Other important limitations to the development of ICI targeting the PD-1 pathway were the low response rates and the need for biomarkers to predict them. Interestingly, serum levels of soluble PD-1 and PD-L1 were lower in cancer patients than in controls. The levels of soluble PD-1 and PD-L1 in serum and the expression of their counterpart in tissues in both tumor center and infiltrate were not correlated. Higher expression of both PD-1 and PD-L1 was associated with the degree of tumor differentiation, presence of necrosis, and tumor size. PD-1 was associated with tumor stage (pT) and PD-L1 was associated with the presence of metastases. Soluble PD-1 and serum PD-L1 were not associated with clinicopathologic parameters, although both were higher in patients with synchronous metastases compared with metachronous metastases, and soluble PD-L1 levels were also higher in patients with metastases compared with patients without metastases. Soluble PD-1 levels were also associated with IMDC prognostic groups in clear cell mRCC, as well as with morphology and response

pattern criteria in patients with metastases who received systemic therapy, mainly TKI. Regarding prognosis, IHC expression of PD-L1 in the tumor center with or without an invasive front was associated with worse survival, as were soluble PD-L1 levels with a threshold value >793 ng/ml [233].

1.3 Influence of tumor histological variant on prognosis and course of metastatic renal cell cancer

RCC is a heterogeneous group of malignant neoplasms arising in the nephron. More than a dozen histologic variants of renal cell tumors have been described (244), but they can vary widely in their genetic, pathologic, and clinical characteristics. The three most common histologic variants of RCC include clear cell RCC, papillary RCC, and chromophobe RCC, which account for 75% to 85%, 10% to 15%, and 5% to 10% of all renal cancers, respectively. One manifestation of the different biological bases and subsequent clinical behavior is the pattern of disease spread in patients with mRCC. The pathways of metastasis to the lung, lymph nodes, bone, and liver in the clear cell variant of mRCC have been well studied [150]. However, the incidence of lesions in less common localizations of metastasis is not well characterized for these subtypes. In addition, the pathways of metastasis in papillary and chromophobe RCC are not as well represented and are not clearly described in the literature. Lymph node involvement and peritonsillar metastases were more common in papillary cancer, whereas liver metastases were more common in chromophobe RCC. In all 3 histologic subtypes, bone metastases were detected in approximately one third of patients. The incidence of metastases to the brain was 8% in the clear cell variant, 3% in the papillary variant, and 2% in the chromophobe variant of the tumor. Compared to clear cell RCC, patients with papillary cancer tended to have lower OS, regardless of the localization of metastases [100].

In terms of histologic type, isolated lung metastasis from luminal and chromophobe variants of RCC was more frequent than combined metastasis involving lungs and other organs. A similar situation was observed for metastases of only light-cell variant of RCC to bone and liver: isolated metastases of this histotype were significantly more frequent than combinations of organs. Metastatic lesions of the brain were significantly more frequent in combination with other organs for all pathologic types [262].

Recently, analysis of the histologic growth patterns of the luminal cell variant of RCC revealed promising correlations with survival outcomes. Six major patterns were identified, as well as 2 evolutionary branches of the clear cell variant: with mesenchymal differentiation (associated with metastasis) and tubuloepithelial differentiation. Based on combinations of which, 3-level and 2-level risk models were developed [117].

Not only the histological type of the tumor, but also the degree of differentiation influenced the indices of OS and PFS. Depending on differentiation, tumors are divided into highly, moderately, and poorly differentiated tumors with different survival times (95, 259). In Haibin Wei (2021), patients with moderately differentiated tumors had better OS than patients with highly differentiated mRCC [262].

All of the above reflected the peculiarities of the biology of different histologic variants of RCC and should be taken into account when planning the tactics of patient management.

1.4 Prognostic differences between synchronous and metachronous with renal cell cancer metastasis

Synchronous metastases were found in approximately 15% of patients with mRCC at initial presentation, and metachronous metastases occurred in 20% of patients without metastases at the time of nephrectomy during dynamic follow-up [229, 246].

It is known that cells of synchronous and metachronous metastases had a different genetic profile [245], which caused different and sometimes unpredictable responses to systemic therapy. Tumor cell activity and tumor burden also differed [248, 249], which caused different response of synchronous and metachronous metastases to targeted therapy, and the variation of 5-year survival rates ranged from 0 to 20%, which was considered unacceptable for most clinicians [29]. Cells forming metachronous metastases probably had fewer oncogenic events than those in synchronous metastases, especially in the primary tumors themselves. Hibernating tumor cells in metachronous metastases exhibited oncogenic activity that stimulated their formation and growth at metastasis sites at some point in time after nephrectomy [245]. Previous immunohistochemical tissue studies have shown that synchronous metastases have different phenotypes with different oncogenic events, which is associated with a worse prognosis in contrast to metachronous metastases [195]. Metachronous metastases were detected early during regular follow-up after nephrectomy, and patients had a lower tumor burden than synchronous metastases [29].

These unpredictable and diverse characteristics of mRCC with different types of metastases are difficult to predict from the primary tumor alone, but easier to predict from combined data from metastatic foci. Therefore, understanding the prognostic differences between synchronous and metachronous metastases is important for developing treatment strategies for mRCC in the era of systemic therapy [13, 85, 255].

The general opinion was that the prognosis in metachronous metastases is better than in synchronous metastases. However, no objective data on this issue have been published, except for some case reports of retrospective studies of metastases to specific organs and genetic analyses of histologic types of RCC [245].

Clinicians require appropriate prognostic data in patients with synchronous and metachronous metastases of RCC for effective systemic therapy. S. Cao et al. proposed three optimal thresholds to consider the period from diagnosis to systemic therapy, 1.1, 7.0, and 35.9 months. Thus, all mRCC cases were divided into four groups: Synchronous metastasis group (time from diagnosis to systematic therapy

≤1.0), early metastasis patient group (1.0< time from diagnosis to systematic therapy ≤7.0), intermediate patient group (7.0< time from diagnosis to systematic therapy <36.0), and late metastasis group (time from diagnosis to systematic therapy ≥36.0 months). The OS and PFS rates differed significantly among the four groups. Patients with longer time from diagnosis to systemic therapy had a better prognosis and promising treatment efficacy. As the time from diagnosis to initiation of systemic therapy decreased, the probability of achieving complete metastasectomy was higher and the prognosis was better [169].

The effect of the number of IMDC risk factors on PFS and OS was analyzed in patients with synchronous and metachronous metastases, divided into subgroups depending on the time of initiation of targeted therapy. An increase in the number of IMDC risk factors had a significant effect on PFS and OS in patients with synchronous metastases when targeting therapy was started within a year. This relationship was not observed for patients with metachronous metastases. The main significant factors in the model were the type of metastases, neutrophilia and anemia [29].

Thus, studying the principles of RCC metastasis can provide clinicians with useful information for each individual patient in terms of diagnosis, prognosis, and other aspects. For example, knowledge of the localization of metastases may be useful for developing personalized examinations for patients with RCC to determine early whether there are other metastases. By integrating clinical and pathomorphologic factors it is possible to create a comprehensive and practical nomogram to assess 1-, 3-, and 5-year prognosis for patients with mRCC.

1.5 Features of the metastatic lesion in metastatic renal cell cancer and its impact on prognosis

Despite the improvement of diagnostic methods, RCC is still often detected already at the stage of metastatic process in 12-16% of patients [34, 230]. Moreover, in 30-50% of patients RCC disseminated at various times after nephrectomy.

1.5.1 Impact of localization of distant metastases on prognosis patients with metastatic renal cell cancer

Because the localization of the metastatic lesion may reflect differences in the biology of the underlying disease, the clinical course of mRCC may vary depending on the nature of the organ involved, even within the same histologic subtype. Indeed, some publications have reported that patients with mRCC with metastases to endocrine organs such as the pancreas may have unusual clinical outcomes, due to the likely favorable biology of the underlying disease [90]. Conversely, metastases to organs such as liver, bone, and/or brain are associated with poor outcomes in patients with mRCC [6, 8, 16, 17, 19, 149, 150].

According to the SEER study, the lungs were the most frequent target of mRCC, with synchronous metastases being identified in 45% of patients [150, 239, 251]. On average, patients were younger and males predominated more frequently. They were frequently observed in patients with pT3 and pN1 grading, while they were less frequent in patients with pT1 and pN0. The degree of tumor differentiation according to Fuhrman did not influence the frequency of lung lesions [262]. In patients in the favorable IMDC risk group who received 1st line therapy without ICI, longer duration of treatment, and isolated metastatic lung lesions correlated with longer OS [189]. Multivariate analysis showed that histologic variant, pT and pN stage, race, presence of nephrectomy, localization of metastases, and tumor size were independent risk factors for the development of lung metastases [5, 168]. Several investigators reported that pT and pN stages were independent prognostic factors [68, 119, 202]. Cox multivariate analysis showed that age, pT and pN stage, presence of nephrectomy, and localization of metastases were independent prognostic factors for OS and CSS rates in patients with mRCC to the lung. Based on these data, three effective nomograms were constructed and validated, which can be used to assist clinicians in assessing the prognosis of lung metastases [168].

Metastases of RCC to bone occurred in only 3.29% of patients at initial diagnosis, but in patients with mRCC they were observed in about one third of cases [11, 133], and bones were affected almost equally often in different histologic variants of RCC [100]. If to achieve the maximum therapeutic effect (to increase survival time and preserve the quality of life) in metastases of most other localizations adequate antitumor therapy is required, in case of metastases of RCC in bones a whole range of additional diagnostic and therapeutic measures should be added to it. Gender and age had no influence on the incidence of bone metastases. In contrast to patients with metastatic lung lesions, bone metastases were significantly frequent in patients with pT1 and pN0. Undifferentiated RCC (Fuhrman grade IV) metastasized to bone most rarely [262].

Patients with liver metastases (23.6%) had poor survival rates [28, 263]. There were no significant differences in age groups of patients with RCC metastases to the liver [262]. Metastases to the liver were most common in women and in patients at stage T4 and N1.

Metachronous brain metastases occurred in 2.4% of patients, although the incidence of brain involvement at the time of RCC diagnosis was 6.5% [88, 134], and were equally common in men and women. Some independent risk factors for brain metastases are similar to those in patients with lung metastases: age at diagnosis and T stage [262]. Significantly more frequent brain metastases occurred in patients at stage pN0. Patients with undifferentiated tumors had a lower incidence of brain metastasis than patients with highly, moderately, and low-differentiated tumors [262]. Low MSKCC risk, sarcomatoid tumor type, and multiple RCC metastases to the brain were prognostic indicators of low OS. At the same time, the time of brain metastases (synchronous or metachronous) did not affect the OS [197], although another group of researchers claimed that the OR for synchronous brain metastases was significantly lower than for metachronous metastases [244].

Combined metastatic lesions have been observed quite frequently in mRCC. In 87.6% of patients, ≥2 sites of metastasis were detected [201]. Metastatic lesion of one organ was detected in 8.1% of patients, and of two organs – in 8.7% [158].

In metastatic lesions of two localizations, combined bone and lung involvement was most frequently observed in 10.82% of patients [262]. Previous studies have shown that there are differences in prognosis depending on the localization, size, and number of metastases in patients with mRCC [258]. The prognosis of patients with liver or bone metastases was worse compared to that of patients with lung or lymph node metastases in both the era of cytokine therapy and targeted therapy [125]. Turkish researchers considered metastatic bone and brain metastatic lesions as independent prognostic risk factors significantly decreasing the OS rates [201].

In the Di Ninno et al. study, of the 12 variables analyzed, 4 were statistically associated with worse OS: number of metastases, presence of liver, bone, or CN metastases, the presence of one or more of which was associated with worse prognosis in both the favorable and intermediate prognosis groups [132]. For patients receiving nivolumab after progression on second and subsequent lines, these factors included IMDC prognosis group, liver and CN metastases at the time of diagnosis [191].

Mekhail et al. reported that the number of metastatic organs as well as other parameters of the MSKCC model were important prognostic factors [278]. Negrieret et al. identified 4 independent factors predicting rapid progression with cytokine therapy: presence of liver metastases, short interval from kidney tumor appearance to metastases (<1 year), presence of more than one metastasis location, and neutrophilosis. Patients with a combination of at least three of these factors had a >80% chance of rapid progression despite treatment [199], making assessment of the localization of RCC metastases an important step in planning personalized therapy.

1.5.2 Number of metastases

According to the literature, both the localization and the number of metastatic foci are of great importance in the prognosis of patients with mRCC. There are single reports on the number and localization of metastatic foci in patients with mRCC [118, 210].

The frequency of solitary metastases was 50.6% compared to 49.4% in two or more localizations [262].

And according to the data of D. Santini et al., metastases in one organ in mRCC were rare [158]. Patients with lung or liver metastases had a higher risk of metastasis to bone compared to patients without metastases in these organs [262]. Patients with mRCC have worse survival with increasing number of localizations of metastases [4, 100, 105, 262]. In another study, patients with multiple metastases had a significant decrease in life expectancy compared to patients with single metastases to parenchymatous organs [69].

1.6 Prognostic models and their modifications for patients with metastatic renal cell cancer

The heterogeneity of mRCC has limited accurate prediction of patient outcomes. There are several clinical tools for predicting mRCC, such as the UCLA integrated Staging System (UISS) [224] or the risk model of the International MRCC Database Consortium – IMDC. D.Y.C. Heng et al., developed a scoring system including various clinical parameters such as Karnofsky performance status, hemoglobin level, corrected calcium and others. Using this scale, they were able to achieve an overall C-index of 0.73 in the prognosis of 645 mRCC patients [195]. In 2001, it was proposed to preliminarily evaluate individual features as a prognostic

model of mRCC MSKCC (Menmorial Sloan Kettering Cancer Center). A set of unfavorable prognostic factors affecting overall survival included: the interval from the initial diagnosis to the start of therapy less than 1 year, somatic status according to the Karnofsky scale <80%, lactate dehydrogenase (LDH) elevation >1.5 times, hemoglobin level <130 g/mL, blood calcium level >10 mg/dL, and no history of nephrectomy. According to this model, patients with mRCC can be assigned to one of three groups. In the group with a favorable prognosis (no unfavorable prognostic factors), the median survival is 26 months, in the group with an intermediate prognosis (1 or 2 factors) – 12 months, in the group with an unfavorable prognosis (3 or more risk factors) – 6 months [138, 154].

Analysis and comparison of the IMDC model with other prognostic models showed that the IMDC and MSKCC models had a high concordance coefficient, with 83% of patients assigned to the same risk group. MSKCC criteria were used more during the era of cytokine use; however, with the emergence of new VEGF therapies in recent years, IMDC criteria have become increasingly recognized and have been used more frequently in modern clinical trials [26]. In sunitinib treatment, multivariate analysis identified five independent predictors of PFS, including serum LDH level, presence of ≥2 metastatic foci, absence of prior nephrectomy, ECOG status, and baseline platelet count; for OS, predictors were serum LDH level, adjusted serum calcium level, time from diagnosis to treatment initiation, hemoglobin level, ECOG status, and presence of bone metastases. For IFN-α-treated patients, LDH level and the presence of ≥2 metastatic foci were predictors of PFS; the factors similar to those for sunitinib-treated patients, except for ECOG status, were predictors of OS, confirming the applicability of the MSKCC model in the era of targeted therapy [196]. It has also been shown that the IMDC prognostic model can be applied to patients who have previously received targeted therapy and not only to patients who have received first-line therapy. The IMDC prognostic model in the setting of second-line targeted therapy had improved prognostic performance and was applicable to a more contemporary cohort of patients than the three-factor MSKCC

model [259]. The IMDC model also demonstrated its prognostic performance in 2-4 lines of therapy in patients treated with ICI [57].

Analysis of 2,315 mRCC patients from the SEER database to construct a nomogram predicting OS in newly diagnosed mRCC patients demonstrated that 8 clinical factors: degree of Fuhrman differentiation, lymph node status, sarcomatoid differentiation, presence of nephrectomy, and bone, brain, liver, and lung metastases were significantly associated with OB. The model outperformed the AJCC staging system (7th edition) [83].

In multivariate analysis, it was found that aspartate transaminase (AST), maximum tumor diameter, and metastasis to lymph nodes were independent variables for PFS. These variables were used in the studies to create nomograms. All calibration plots showed excellent model prediction accuracy. The C-indices of the nomograms for predicting OS, cancert-specific survival, and PFS were 0.729 (95% CI, 0.659-0.799), 0.725 (95% CI 0.654-0.796), and 0.702 (95% CI 0.626-0.778), respectively [82].

Researchers from Winship Cancer Institute conducted a retrospective review of 87 patients with mRCC who received cabozantinib from 2015 through 2019 in second and subsequent lines of therapy. Elevated baseline monocyte-to-lymphocyte ratio, sarcomatoid histologic component, ECOG >1, and absence of bone metastases were each assigned 1 point to create a prognostic model. A three-group risk scoring system was then established: low (score =0-1), intermediate (score =2), and high risk (score =3-4). It was shown that high- and intermediate-risk patients had significantly shorter OS and PFS compared with low-risk patients [170].

Japan Urologic Oncology Group also proposed a prognostic scale for patients receiving axinitib in second-line treatment. The following factors in this cohort were independently associated with low OS in multivariate analysis: low Karnofsky status, <1 year from diagnosis to targeted therapy, neutrophilosis and low albumin levels, elevated CRP and LDH. This model outperformed the IMDC and MSKCC scales in its predictive ability [104].

In a multicenter retrospective study, S.E. Rebuzzi et al. examined the prognostic role of peripheral blood inflammation scores and clinical factors to develop a new prognostic scale for patients with mRCC receiving at least second-line nivolumab. In single-factor and multivariate analyses, all inflammation scores, IMDC score, and bone metastasis were significantly correlated with OS scores. The multivariate model including neutrophil-to-lymphocyte ratio, IMDC score prognosis, and presence of bone metastases had the highest C-index (0.697) and was selected to develop the Schneeweiss scoring system, after which five categories of patients with different OS were identified. Moreover, the Meet-URO score allowed accurate risk stratification for all three IMDC groups, making it easily applicable in clinical practice without any additional costs [136].

In the work of L. Wei et al. showed that the prognosis of patients with non-small cell variants of RCC is inherently worse than that of patients with light cell variant, however, given the small number of these variants, it is quite difficult to collect a base for evaluating prognostic factors. For cancer of the collecting tubes, 15 selected variables were identified as factors that may affect patient survival, such as age at diagnosis, stages T, N and M, tumor size, degree of differentiation, presence of nephrectomy, radiation therapy and chemotherapy. Nine clinicopathologic characteristics were identified as risk factors using single-factor Cox regression and were the factors with the highest score in terms of their importance; they were also found to have a significant impact on patient survival. In addition, several studies have reported the influence of non-clinical factors on the prognosis of the disease. In this study, we analyzed the clinicopathological characteristics and prognosis of patients with this histological type of RCC using a novel artificial intelligence algorithm to construct three prognostic models [25]. The estimated 1-year, -3-year, and 5-year OS and CSS rates in the analytic cohorts were 56.4% and 60%, 32.5% and 37.3%, and 28.7% and 33.6%, respectively. Using these factors, a nomogram with relatively good discriminability and calibration was developed. The C-index was 0.764 and 0.783. Patients were categorized into low-risk, intermediate-risk, and high-risk groups according to the total score calculated from the nomogram.

The calibration curves showed a good agreement between the predicted and actual probability associated with OS and CSS [192]. According to the study by L. Zhou et al., pT and anemia were independent prognostic factors for collecting tube mRCC [64].

For patients with sarcomatoid RCC, age at diagnosis, stage pT, stage pN, bone metastases, liver metastases, lung metastases, and nephrectomy have been identified as independent predictors of OS [70]. Also, sarcomatoid differentiation, hypercalcemia, elevated serum CRP levels and the presence of liver metastases were associated with primary refractory mRCC in patients receiving first-line ICI therapy [188].

The intermediate-risk group according to the International MMRCC Database Consortium (IMDC) criteria is considered to consist of patients with different prognosis, which is approximately 52% according to the IMDC model. In a retrospective analysis of patients in IMDC, the proportion of patients who achieved long-term survival (OS ≥4 years) was 38% versus 14% for intermediate prognosis patients with 1 risk factor compared with patients with 2 risk factors. IMDC prognostic factors such as neutrophilia, thrombocytosis, and hypercalcemia were present in <5% of patients with an OS ≥4 years, whereas in patients with an OS ≤6 months, Karnofsky status <80% and anemia were identified in a large percentage of cases. This difference in responses raised the question of whether patients with one risk factor should be treated in the same way as patients with two risk factors [55]. In accordance with the IMDC model, after combined ICI+TKI first-line therapy, K. Takahara et al. performed a multivariate analysis of the six factors included in the IMDC model for patients in the intermediate-risk group, demonstrating that low Karnofsky status, anemia, and thrombocytosis were independent predictors of low OS. The intermediate risk group was subsequently divided into the following two groups (intermediate prognosis 1 and 2) according to the three independent predictors of OS in patients receiving targeted therapy [207].

In a study by J. Teishima et al. found the influence of systemic immune inflammation index (SII), which was calculated based on the number of neutrophils,

platelets and lymphocytes, on the prognosis of patients with mRCC. The threshold value of the index was 730. The 50% OS in the high SII group was 21.4 months, which was significantly worse than that in the low SII group (49.7 months; $p<0.0001$). Multivariate analysis showed that high SII was an independent prognostic factor for lower OS. Further construction of a modified IMDC risk model that included SII instead of neutrophil and platelet counts allowed reclassification of all mRCC cases into four groups with a 50% OR of 88.8, 45.9, 29.4, and 4.8 months, respectively [130].

Thus, the group of intermediate prognosis mRCC patients is heterogeneous in nature, had different clinical outcomes when treated, moreover, the outcomes of patients with one risk factor were significantly different from those of patients with two risk factors [116], which has constantly prompted researchers to search for new prognostic factors for patients in the intermediate risk group.

The use of mGPS in conjunction with the IMDC model allows stratification of mRCC patients receiving first-line TKI. The median OS in the high and low mGPS patient groups was 38.4 months and 5.6 months, respectively. Multivariate analysis showed that high mGPS, multiple metastases, and hypercalcemia were independent prognostic factors for decreased OS in the intermediate prognosis subgroup. Patients with high mGPS had significantly worse OS rates than those in the low mGPS subgroup (21.0 months and 33.7 months). Comparing the OS of patients with high mGPS, no significant differences were found for patients in the intermediate- and low-risk groups [127].

Several studies have reported different outcomes of patients with mRCC depending on the nature of metastasis. It was noted that liver metastases were often found in patients with a poor prognosis according to IMDC criteria. In addition, the risk ratio for death (adjusted for IMDC risk factors) was 1.4 for patients with bone metastases and 1.42 for patients with liver metastases. IMDC data were also used to assess the outcome of patients with brain metastases, of which only 12% fell into the IMDC favorable prognosis group [149].

As described by Schmidt et al, 3 parameters including time from diagnosis to systemic therapy <3 vs ≥3 years, Karnofsky status 80 vs >80, and presence of brain, liver, or bone metastases were used to divide the favorable IMDC prognosis group into 2 new categories: very favorable and favorable prognosis groups (44 (39.3%) and 68 (60.7%)) [266]. The median OS (55.8 months vs 34.2 months) was longer in the very favorable risk group than in the favorable risk group. The fit index for the new IMDC model in all patients was 0.65 for the OS [103].

C. Franzese et al. introduced an OS stratification scale for patients with oligometastatic renal cancer receiving stereotactic radiotherapy and systemic therapy for up to five metastases. The most common localization of metastases was brain (34.71%), followed by lung (25.62%). With a median follow-up of 19.4 months, 1- and 3-year OS were 82.62 and 55.11%. Class 1 included patients aged ≤65 years treated for extracranial metastases, with a 3-year overall survival of 82.66%. Class 2 included patients aged >65 years, without a history of bone metastases, treated for extracranial metastases, with a 3-year OS of 67.91%. Patients aged >65 years and with a history of bone metastases treated for extracranial metastases were categorized as class 3 with a 3-year OR of 37.5%. Class 4 included patients treated for brain metastases with a 3-year overall survival of 9.70% [225].

Korean Renal Cancer Study Group (KRoCS) proposed a model to stratify patients with mRCC into 3 risk groups: favorable (0), intermediate (1-2), and poor (3 or more) according to the number of prognostic factors. Seven variables such as more than 2 localizations of metastases, no prior nephrectomy, ECOG status ≥2, anemia, hypercalcemia, neutrophilosis, and high alkaline phosphatase levels were identified as prognostic factors for low OS. The median OS was 61.1 months in the favorable group, 26.5 months in the intermediate group, and 6.8 months in the unfavorable group. According to the results of comparisons, the KRoCS model demonstrated superiority over the MSKCC and IMDC models for patients with luminal variant of mRCC [194].

Over the past decade, modern immunotherapy has transformed the efficacy of mRCC treatment, prompting a reconsideration of prognostic stratification of

prognosis based on the model developed by Heng in the TKI era. As a preliminary screening, prognostic factors such as age, gender, race, and IMDC prognostic group may be important for mRCC patients receiving TKI. Patients older than 70 years of age had better OS compared to younger patients. Although some researchers reported that compared with younger patients at diagnosis (<57 years), older age at initial diagnosis was an unfavorable factor for patients with mRCC [119]. Similar to the aforementioned study, Cox regression analysis in this study showed that the older the patient's age, the worse the prognosis. Non-Caucasians receiving ICI had worse OS and PFS compared to Caucasians. Males had a poorer OS than females. Compared to the IMDC favorable prognosis group, the OS in the unfavorable prognosis group was worse [160].

S. Sagie et al. studied prognostic factors in 127 patients receiving ICI therapy for mRCC (median OS was 57 months). Five factors were associated with a low OS: no nephrectomy, liver metastases, less than one year before treatment, thrombocytosis, and Karnofsky status less than 80% (model C-index of 70.7 compared to an estimate of 62.0 for the IMDC model). Based on these criteria, it has been proposed to divide patients into low-risk groups (0-1 risk factors) and high-risk groups (when 2-5 risk factors are present) [214].

The median OS was significantly lower in patients treated with ICI with platelet-to-lymphocyte ratio >204 than in patients with platelet-to-lymphocyte ratio ≤204 (14.6 months vs. 31.6 months). In addition, the presence of brain metastases and the IMDC prognostic scale were identified as independent prognostic factors for OS [261].

Another risk assessment system was created for patients with mRCC receiving ICI. The monocyte-to-lymphocyte ratio, body mass index, and the number and localization of metastases at baseline were used to select a variable in the multivariate model to calculate the risk score. Patients were categorized using four-level risk groups into good prognosis (risk score =0), intermediate (risk score =1), poor (risk score =2), or very poor (risk score =3-4). This scale has greater consistency with Uno than IMDC [171].

While prognostic clinical nomograms can be useful, they can be cumbersome to use and often involve only a sampling of available information – both of which potentially limit their effectiveness. Artificial intelligence and machine learning can be extremely useful for utilizing this highly complex data to predict clinically relevant outcomes such as survival or response to therapy [156].

1.7 Neural networks

Artificial intelligence is increasingly being applied to various medical problems, achieving promising results in various branches of medicine [42, 63, 80, 96]. In today's world, the use of artificial intelligence can be useful in predicting the outcome of systemic therapy for mRCC, and this is particularly important as there is an urgent need for reliable prognostic biomarkers in this disease. An integrative approach can be used to identify patients with favorable and unfavorable prognosis who are more suitable for systemic therapy or surveillance [156]. The use of ultra-precise neural networks in the work of Ning et al. was performed to predict the prognosis of clear cell mRCC based on the determination of radiologic and pathomorphologic data [137].

1.8 Current approaches to the treatment of metastatic renal cell cancer

Prognostic models that integrate clinical features and molecular biomarkers with predictive value are guaranteed to help clinicians in their decision-making process and offer patients the most effective therapy as part of a personalized, precision medicine-based therapeutic strategy.

1.8.1 Impact on the prognosis of patients with metastatic renal cell carcinoma surgical treatment of the primary tumor and metastases

1.8.1.1 Cytoreductive nephrectomy and its role in the treatment of patients with metastatic renal cell disease cancer at the present stage

Nephrectomy is clearly the standard for localized renal cancer; historically, its role in the treatment of metastatic disease has been less well defined. This changed when prospective studies in the early 2000s showed the benefit of CN prior to systemic therapy [79, 213]. Thus, surgery became an important point in the treatment of patients with mRCC. The first studies prospectively demonstrated the benefit of patients after CN followed by systemic therapy compared to systemic therapy alone. In the EORTC-30947 study, nephrectomy combined with interferon-α (IFN-α)-based immunotherapy for mRCC resulted in a 10-month longer OS compared with a group of patients without CN (17 vs. 7 months) [213]. CN could be beneficial given that tumors may suppress immune responses. Large primary tumors can lead to suppression of T-cell function, and previous studies have demonstrated the inability of systemic agents to induce significant responses in primary tumors of patients with mRCC [53].

Recently, however, the role of CN for the prognosis of patients with mRCC has been questioned, especially in the era of targeted therapy. A large randomized phase III study evaluated the efficacy of sunitinib in mono-regimen or after CN in mRCC [237] and demonstrated no less efficacy of sunitinib compared to the combination of CN+sunitinib, but in patients with an intermediate or poor prognosis. In the 2019 SUPTIME trial, delayed CN in combination with targeted therapy was shown to contribute to an increased OS compared to performing CN followed by targeted therapy. However, the extent of tumor burden, including the primary tumor, was an important prognostic factor. This meant that mRCC with TKI therapy after nephrectomy was associated with similar prognosis regardless of the type of

metastasis. Reduced tumor burden after removal of the primary tumor lesion, provided better prognostic outcomes when targeting therapy was administered. However, the presence of a good somatic status of the patient and a primary tumor representing >75% of the total tumor burden in the absence of metastatic CN or liver involvement did not improve the prognosis of patients with mRCC after CN, resulting in a lower incidence of their discharge [29]. Several investigators reported that CN did not significantly improve the survival of patients with multiorgan metastasis of mRCC, but instead was associated with higher mortality rates in the first 6 months after surgery [53].

Given these equivocal results, patient selection has been crucial in the decision for CN for mRCC, and in appropriately selected patients, CN has continued to be an important treatment option. This is particularly important for slow-growing metastases, where long-term follow-up until progression can be achieved and systemic therapy can be used effectively at this stage [35].

Thus, the analysis of retrospective data showed that delayed CN has a potential therapeutic effect in a subgroup of patients with favorable tumor response to the combination of nivolumab plus ipilimumab for a certain period of time. But this study requires a prospective randomized clinical trial to confirm the prognostic impact of delayed CN after ICI in synchronous mRCC [267]. More recent studies have shown that CN should not be offered to all patients; it may be of value in patients with a limited number of IMDC prognostic factors.

1.8.1.2 Metastasectomy options and its role in treatment of metastatic renal cell cancer

The role of metastasectomy in mRCC is also not clearly defined. Despite the lack of randomized controlled trials, the benefits of metastasectomy in terms of OS and CSS have been demonstrated in large observational studies. The results

of ongoing clinical trials evaluating the impact of the combination of metastasectomy and systemic therapy could shed light on a new armamentarium of treatment in this subgroup of patients [172]. Although evidence supporting the role of complete metastasectomy in mRCC was mainly obtained in the era of cytokine therapy, complete metastasectomy for RCC was associated with improved CSS in the post-cytokine era: two-year CSS was significantly higher in patients with complete metastasectomy compared to the group without (84% vs. 54%, $p<0.001$) [67]. Metastasectomy continues to be used in patients with solitary or single metastases of RCC. With the introduction of newer systemic therapies for mRCC, the performance of metastasectomy has become more widely performed because most patients have an incomplete response to systemic treatment [89]. In general, most studies demonstrated that complete cytoreduction was associated with improved clinical outcomes. A large study conducted by K. Wu et al. in 2020 using data from 2.911 patients with mRCC showed that performing metastasectomy was associated with a significant reduction in cancert-specific mortality (3-year cumulative incidence 52.6 vs. 59.2%) [167]. However, it is important to note that these retrospective studies were subject to selection bias. Many patients who underwent metastasectomy may have been selected from the general population based on quality of life and tumor resectability. Russo et al. demonstrated that 91 patients with synchronous mRCC who underwent CN had median OS of 30 and 12 months with and without metastasectomy [76]. Therefore, another important factor to consider in determining whether patients would benefit from metastasectomy was the number of metastases: oligometastatic or multiple lesions. Although no study has specifically defined a limit on the number of metastases for these two groups, authors have agreed that if more than 2 metastases are present, the likelihood of complete metastasectomy as well as OS decreases [28, 62].

Metastasectomy is possible in a small proportion of patients with oligometastatic RCC with liver or pancreatic involvement. Median OS after liver resection ranged from 16 to 142 months, and 5-year OS ranged from 14.7 to 62%. After pancreatic resection, median OS ranged from 6 to 106 months, and 5-year OS

ranged from 26 to 88%. Metachronous metastases and longer PFS after resection of the primary tumor were associated with better survival rates. Mortality rates after liver and pancreatic resection were 2.7% and 4.2%. Therefore, it was thought that resection or ablation of the liver or pancreas for oligometastatic RCC may benefit a very select group of patients [264]. Several retrospective studies have shown the benefit of metastasectomy in mRCC with isolated pulmonary metastases. In those patients who cannot benefit from surgery, stereotactic radiation therapy or radiofrequency therapy should have been considered. Despite the lack of randomized trials, metastasectomy for lung lesions was the most effective [212]. In 2016, D.W. Langerhuizen et al. reported that patients with mRCC metastases to bone who underwent complete or partial metastasectomy showed a significant difference in survival with complete removal of metastases [148]. In 2019, S.H. Kim et al. analyzed 117 patients with mRCC metastases to bone and found that both PFS and OS rates were significantly higher in patients after complete metastasectomy compared to patients without [28]. The median PFS in the groups was 17.79 and 8.71 months, and the median OS was 31.89 and 9.65 months, respectively [243].

M. Sun et al. also evaluated the survival of patients with brain metastases of mRCC who underwent metastasectomy compared to those who did not undergo it. The 1-, 2-, and 3-year OS rates were 71.1%, 51.2%, and 41.3% versus 46.8%, 36.2%, and 29%, respectively. Brain metastases in mRCC have a poor prognosis and metastasectomy in this patient population may improve survival rates in selected patients [190].

Thus, metastasectomy has been demonstrated to be associated with improved clinical outcomes in mRCC. However, these outcomes are influenced by multiple factors, including patient risk stratification, localization, type of metastases, and the ability to resect metastases. The decision to perform metastasectomy should be based on multiple factors, including patient health status, age, disease progression, and metastasis localization. Other prognostic factors, including histologic and molecular analyses, may further influence the selection of patients for metastasectomy as more research is conducted in this area. As the arsenal of systemic therapies continues

to expand, it is important to continue to evaluate metastasectomy in terms of patient survival and the use of systemic therapy after metastasectomy.

1.8.2 Current understanding and possibilities of systemic therapy metastatic renal cell cancer

1.8.2.1 Molecular genetic basis of systemic therapy metastatic renal cell cancer

Renal cancer is a malignant tumor that develops from the epithelium of the proximal tubules and collecting ducts (renal cell carcinoma) or from the epithelium of the calyx-lochanous system (transitional cell carcinoma), the pathogenesis of which is a complex and multistep phenomenon.

Light-cell RCC is the most common histologic subtype. It is characterized by loss of the Hippel-Lindau (VHL) gene, hypoxia-inducible factor (HIF) and vascular epithelial growth factor (VEGF). A defect in one allele of the VHL gene is inherited in patients with VHL syndrome, and a defect in the other allele is acquired in the affected organ. Acquired defect in both alleles of VHL was observed in the majority of patients with sporadic/nonhereditary clear cell RCC, resulting in dysfunction of the VHL protein [222]. Alterations in the VHL tumor suppressor gene on chromosome 3 could be seen in 90% of cases of clear cell RCC [231]. Disruption of the VHL gene resulted in a pseudohypoxic status that promoted angiogenesis. Increased accumulation of HIF led to the production of pro-angiogenic factors, namely VEGF, platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). HIF also induced the activation of MET and AXL (proangiogenic factors), which supported tumor cell growth, invasion and metastasis [142]. The introduction of anti-angiogenic TKI therapy has improved the prognosis of many patients. However, its efficacy is

limited due to the development of therapy-resistant cell clones resulting from the activation of the alternative pathway of angiogenesis [252].

Ongoing studies have indicated that inactivation of VHL is not sufficient to induce RCC formation. Additional genetic events and cellular alterations are required as second hits during malignant transformation. Comprehensive genomic analysis of luminal RCC identified epigenetic control and the PIHC target of rapamycin (mTOR) pathway as major determinants in the pathogenesis of luminal RCC. In this histologic variant, the mTOR pathway is usually hyperactivated [115]. The dysregulation of mTORC1 signaling played a key role in oncogenesis and progression of the luminal cell variant of RCC, and mTOR hyperactivation correlated with poor outcome. The mTOR pathway can be activated by cancer cells through various mechanisms, including loss of p53, mutations in PI3K components and paracrine growth factor production, or through mTOR complexes such as TSC1/2, PTEN, and Lkb1. Consequently, mTOR inhibitors (such as everolimus and temsirolimus) have been approved for the treatment of mRCC, but most patients rapidly develop resistance to therapy [187].

In contrast to cytokine therapy, recently developed targeted therapies have focused more on treating the highly vascularized or immune-associated tumor microenvironment [153, 245]. In the tumor microenvironment, cancer cells can evade immunological surveillance by altering their surface antigens, thus avoiding detection and destruction by host lymphocytes. A central mechanism of tumor-induced immune suppression was the increased expression of ligands capable of binding inhibitory T cell receptors [140]. At the tissue level and in the tumor microenvironment, immune escape of cancer cells was mediated by inhibitory PD-1 signaling. Normally, the PD-1 receptor (PDCD1 or CD279) is expressed on effector T cells, B cells and NK cells, while its ligands PD-L1 and PD-L2 were expressed in various intrinsic cell types (such as epithelial tubules, endothelial cells, fibroblastic reticular cells, pancreatic islet cells, astrocytes, neurons), thus avoiding autoimmunity and host organ damage. An even more important feature was on T cells expressing PD-1 "depleted" lymphocytes that had previously experienced high levels of stimulation.

This state of depletion was frequently observed in chronic infections, cancer and characterized by impaired T cell function [280]. On the other hand, cancer cells strongly upregulated PD-L1 ligands, and in metastatic tissues, the PD-1 pathway on memory T cells caused T cell deactivation. Increased PD-L1 expression was evaluated on the cell surface in several cancer types, including melanoma, bladder, lung, kidney, colon, ovarian, breast, glioblastoma, multiple myeloma, and T-cell lymphoma. The underlying mechanism associated with enhanced PD-L1 expression in tumor cells has been correlated with PTEN deletion [147], PI3K signaling, and persistent high levels of IFN-y in the tumor microenvironment [181]. In normal physiological cells, PD-1 programmed death ligand and cytotoxic T lymphocyte associated antigen-4 (CTLI-4) attenuated T cell activation and are vital for maintaining the immunological balance between self-defense and self-tolerance [181]. PD-L1 expression by tumor cells may contribute to their immune tolerance, hence PD-1/PD-L1 and CTLA-4 blockers may enhance the antitumor response of CD8 T cells [87]. Blocking PD-1, PD-L1 and PD-L2 signal transduction by monoclonal antibodies allowed re-activation of tumor-infiltrating lymphocytes to detect and kill malignant cells. Originally discovered by Y. Ihshida et al. [135] as an immunoglobulin expressed on dying thymocytes, PD-1 later became associated with suppression of the T-cell response. Currently, the FDA has approved several monoclonal antibodies targeting PD-1 (i.e., pembrolizumab, nivolumab, and cemiplimab) and the PD-L1 ligand (atezolizumab, avelumab, and durvalumab) for the treatment of several different malignancies, including mRCC. Thus, one CTLA-4 inhibitor and five PD-1 / PD-L1 inhibitors have been approved by the FDA, and others are being tested in phase 3 clinical trials [265].

However, different pathophysiologic microenvironment and immune-related conditions in different types of metastasis induce different therapeutic responses to targeted therapies in the clinical context of mRCC. An integrated evaluation of 823 tumors from patients with advanced mRCC identified molecular subsets associated with different clinical outcomes when angiogenesis is blocked alone or with ICI. Uncontrolled transcriptome analysis identified seven molecular subsets with

different angiogenesis, immunity, cell cycle, metabolism, and stromal cell programs. For example, the combinations of sunitinib and atezolizumab + bevacizumab were effective in subgroups with high angiogenesis; atezolizumab + bevacizumab improved clinical efficacy in tumors with high T effector and/or cell cycle transcription. Somatic mutations in PBRM1 and KDM5C are associated with marked angiogenesis and AMPK/fatty acid oxidation gene expression, while CDKN2A/B and TP53 alterations are associated with enhanced cell cycle and anabolic metabolism. Sarcomatoid tumors showed a lower prevalence of PBRM1 mutations and angiogenesis markers, frequent CDKN2A/B alterations and increased PD-L1 expression. These results can be applied to molecular stratification of patients, to explain the improved outcomes of sarcomatoid tumors using ICI compared to antiangiogenic drugs alone, and to develop personalized therapies for RCC [152].

Thus, by selecting patients for current standard therapies, IMDC risk stratification represents the most valid tool in this regard. Nevertheless, research to identify molecular characteristics that may lead to more personalized approaches is ongoing. Markers that have demonstrated consistent prognostic value in other cancers treated with ICI, such as PD-L1 expression in tumor cells and in immune cells and tumor mutational burden, have failed to yield similar results in mRCC.

1.8.2.2 Basic principles of systemic therapy metastatic renal cell cancer

Improved understanding of the pathogenesis of mRCC has revolutionized treatment since 2005 in two ways. First, there has been an increased understanding of the vital role of angiogenesis facilitated by VEGF inhibitors, followed by the success of ICI emphasizing the immunogenicity of mRCC cells.

Inhibitors of the mammalian target of rapamycin (mTOR)

The permanently activated mTOR signaling pathway played an important role in the oncogenesis of RCC, and mTOR inhibitors, also known as rapamycin analogs, inhibited mTOR phosphorylation, resulting in altered translation of matrix RNA, which encodes proteins involved in cell survival, cell proliferation, and angiogenesis [145]. The mTOR inhibitors everolimus and temsirolimus have been used in routine clinical practice since 2009. Temsirolimus, an mTOR inhibitor, was compared with IFN-α in a three-component, first-line phase III Global Advanced Renal Cell Carcinoma trial including mRCC patients with poor prognosis, dividing them into treatment groups of temsirolimus, IFN-α, and a combination of temsirolimus and IFN-α. The temsirolimus group showed a higher OS compared with IFN-α, although the combination treatment did not have the same effect [253]. Temsirolimus is effective and indicated for use in patients with intermediate and especially poor prognosis in first-line systemic therapy [157].

Proangiogenic factors

TKI such as sunitinib and sorafenib have been available since 2006, followed by second-generation TKI such as pazopanib, axitinib, cabozantinib, lenvatinib, and tivozanib. Although an increasing number of urologists and oncologists are focusing on the efficacy of immunotherapy or immunotherapy in combination with targeted therapy in mRCC, as TKI were recently found to significantly improve disease outcomes, targeted therapy remains the cornerstone of systematic treatment of mRCC. Sunitinib (Sutent; Pfizer, New York, NY, USA) and pazopanib (Votrient; Glaxo, Brentford, UK) were the first-line drugs approved by the CFDA, and long-term prognosis data are largely based on the use of targeted therapy. Sunitinib is an orally administered TKI that targets several receptors including VGFR types 1-3, PDGFR-α, PDGFR-β, c-KIT and FMS-like tyrosine kinase [36]. Pazopanib is another BNR targeting the same receptors except for FMS-like tyrosine kinase [183]. According to the results of randomized phase III studies, both tyrosine kinase inhibitors improved the prognosis of mRCC in terms of OB or UBP: sunitinib in a phase III study showed a significant improvement in median UBP compared to IFN-α

drug therapy (11 months versus 5 months) and a PFS of 31% versus 6% in favor of sunitinib [238]. In a placebo-controlled phase III trial, pazopanib improved PFS in patients with favorable and intermediate prognosis who were untreated or receiving cytokines (median PFS 11 months versus 2.8 months) [27, 183]. When pazopanib and sunitinib were compared in the COMPARZ phase III study, pazopanib was non-inferior to sunitinib with similar UBP rates [184]. Given their comparable efficacy and safety profiles, both sunitinib and pazopanib are indicated as first-line agents in patients with a favorable prognosis.

Cabozantinib is an oral TKI targeting VEGFR in addition to MET and AXL, therefore resulting in simultaneous suppression of metastasis, angiogenesis and tumor growth [52]. Compared to sunitinib, cabozantinib demonstrated an increase in not only PFS (8.2 vs. 5.6 months; HR 0.66; 95% CI 0.46-0.95) but also PFS (33% vs. 12%) [51]. Cabozantinib was then approved as a first-line option for the treatment of mRCC on December 19, 2017.

Axitinib, an oral TKI and potent VEGFR inhibitor, has demonstrated clinical efficacy as a second-line treatment for patients with mRCC. In a randomized phase III study, patients with ineffectiveness of first-line therapy with sunitinib/bevacizumab with INF-α or temsirolimus were randomly assigned to receive either axitinib or sorafenib. Although the median OS was similar in both treatment groups, PFS was 6.7 months vs. 4.7 months (OR 0.67; 95% CI 0.54-0.81) and PFS (19% vs. 11%) in the population receiving 2nd line targeting therapy favored axitinib over sorafenib [46, 65]. These results demonstrated that axitinib is a second-line treatment for mRCC.

Other approved systemic therapies included selective monoclonal antibodies such as bevacizumab directed against VEGF, which also inhibited angiogenesis and therefore inhibited tumor growth [163]. However, after the favorable results of immunotherapy combination studies (ipilimumab plus nivolumab) and the current success of immunotherapy combinations with VEGF inhibitors, the role of some of the above-mentioned drugs as single agents is less significant and effective only in certain circumstances, for example, in cases of absolute contraindications to the use of ICI.

Therapy with checkpoint inhibitors

More recently, the emergence of ICI targeting PD(L)-1 or CTLA-4 has revolutionized systemic therapy for clear cell mRCC. For clinical use, nivolumab became available as monotherapy in 2016 and in combination with ipilimumab/nivolumab starting in 2019. Combinations of TKI and ICI have only recently been explored and utilized. Humanized monoclonal antibodies target inhibitory receptors (e.g., CTLA-4, PD-1, LAG-3, TIM-3) and ligands (PD-L1) expressed on T lymphocytes, antigen-presenting cells, and tumor cells, and induced an antitumor response by stimulating the immune system. Also, checkpoint inhibitors significantly prolonged patient survival. Nevertheless, the improvement in OS was complicated by the occurrence of immune-related side effects [265]. Although a significant clinical advantage was reported in patients with PD-L1-negative tumors (better survival rates), greater efficacy of ICI was observed in patients with PD-L1-positive tumors [220].

ICI have demonstrated impressive activity in clear cell mRCC and have become standard treatment options for patients with disease progression. Data for non-small cell tumor variants are more limited. However, in the era of targeted therapies and immunotherapy, drug costs are increasing dramatically. For this reason, it is necessary to evaluate not only the efficacy of treatment but also its cost. In a recent study, the combination of nivolumab and ipilimumab was evaluated in terms of cost-effectiveness compared with sunitinib [106]. In this study, the immunotherapy combination had an economic benefit associated with product efficacy. Furthermore, this cost-effectiveness seems to be most interesting in patients expressing at least 1% PDL1. Finally, the development of new ICI allowed the presentation of new therapeutic combinations [43].

1.8.2.3 Peculiarities of systemic therapy depending on from the localization of metastases

Researchers have outlined some of the features of systemic therapy pertaining to specific anatomic regions. In particular, bone and brain metastases present significant therapeutic dilemmas. Recent data indicated a potential benefit of cabozantinib for patients with bone metastases. It was previously demonstrated that cabozantinib, had marked activity in prostate cancer metastases to bone [50]. Cabozantinib was compared with everolimus in a phase III clinical trial, demonstrating an improvement in PFS in patients with bone metastases (7.4 months with cabozantinib vs. 2.7 months with everolimus) [94]. It was also noted that cabozantinib caused a more pronounced decrease in bone tissue regeneration markers such as N-telopeptide.

The CN is thought to represent a "safe haven" for RCC metastases; as preclinical studies suggest that drugs such as sunitinib and sorafenib cannot fully penetrate the blood-brain barrier [48]. A phase III study of temsirolimus demonstrated that the drug penetrates the brain, in contrast to previously published studies regarding TKI. Temsirolimus monotherapy improved OS compared to IFN-α, which provided the rationale for prescribing temsirolimus as first-line treatment in the study cohort of patients with brain metastases.

Retrospective reviews evaluating the safety and efficacy of TKI for mRCC with brain metastases have been conducted. One study identified 65 patients with RCC metastases to the brain. The vast majority (80%) received VEGF-ITK therapy, with very limited neurologic side effects. A total of five patients experienced neurologic side effects: radiation necrosis and metastasis hemorrhage [149]. In the second-line setting, the current clinical debate has centered on the use of either cabozantinib or nivolumab. Like cabozantinib, nivolumab was evaluated in a phase III comparison with everolimus in patients previously treated with TKI therapy [166]. It was observed that nivolumab improved both OS and overall response rate (ORR)

compared to everolimus. However, it is worth noting that the phase III evaluation of the nivolumab trial did not include patients with brain metastases, whereas the phase III evaluation of cabozantinib did. Thus, in the second-line setting, cabozantinib may be the drug of choice for patients with CN metastases. Nivolumab is the standard of care for patients with clear cell mRCC after failure of antiangiogenic therapy, but its activity against brain metastases remains unknown because these patients have been excluded from pivotal trials. In a study by R. Flippot et al. patients with asymptomatic brain metastases were prospectively identified and underwent a dedicated brain examination. Two cohorts were formed: cohort A included patients with previously untreated brain metastases (39 cases), and cohort B included patients whose brain metastases had been previously treated with therapy (34 cases). The primary endpoint was the rate of intracranial response in Cohort A. The rate of intracranial response was 12% in Cohort A; no objective response was reported in patients with multiple brain lesions or larger than 1 cm. Median PFS was 2.7 months in cohort A and 4.8 months in cohort B, with an adjusted risk ratio of 2.04. The OS at 12 months was 67% in Cohort A and 59% in Cohort B. The majority of patients in Cohort A (72%) required subsequent focal brain therapy, so the activity of nivolumab is recognized as limited in patients with untreated brain metastases [226].

At the American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium (American Society of Clinical Oncology (ASCO)) 2016, an analysis of OS and response in key subgroups (based on risk groups, number of sites of metastasis, sites of metastasis, months of prior therapy, and type and amount of prior therapy) was presented. The efficacy of nivolumab was found in patients with both liver and bone metastases, as well as in patients with one or two/more foci of metastasis [56].

1.8.2.4 Peculiarities of systemic therapy depending on from the histologic variant of metastatic renal cell cancer

The majority of studies evaluating the efficacy of systemic therapy have focused on luminal variants of mRCC as the most common histologic variant. However, the most unfavorable prognosis and difficulties in treatment are observed for non-small cell variants.

A retrospective analysis of 1.145 patients based on the mRCC databases (IMDC) was performed to assess the outcomes of patients with advanced non-small cell RCC. Patients were categorized into three groups according to first-line therapy: ICI-based therapy (monotherapy or combination), TKI monotherapy, or mTOR inhibitor monotherapy. Papillary RCC was the most common subtype (54.9%). For first-line therapy, 74.3% received TKI monotherapy, 15% received mTOR inhibitor monotherapy, and 10.7% received ICI-based therapy. The median OS in the ICI group was 28.6 months, compared with 16.4 months in the TKI group and 12.2 months in the mTOR group. The PFS was 27.2% in the ICI group, 14.5% in the TKI group and 9% in the mTOR inhibitor group, which identified ICI as the drugs of choice for first-line therapy of non-small cell mRCC [176]. The combination of atezolizumab and bevacizumab has not been approved by the FDA as first-line therapy for non-small cell mRCC.

In patients with sarcomatoid histologic differentiation, an aggressive form of RCC with poor prognosis, median PFS was 8.3 compared to 5.3 months in the atezolizumab plus bevacizumab versus sunitinib group, and median OS was not reached for the combination compared to 15.0 months in the sunitinib group. The combination also demonstrated a higher PFS of 49% compared to 14% for sunitinib [41]. The better efficacy of ICI agents compared to sunitinib in terms of PFS and complete response rate was in patients with sarcomatoid tumor type [175]. Currently, it appears that the combination of ipilimumab in combination with nivolumab is promising in sarcomatoid differentiated mRCC, for which PD1/PD-L1 expression

is more intense than in patients with the clear cell variant of RCC. Based on these encouraging results, the experts agreed that nivolumab in combination with ipilimumab should be used in the treatment of sarcomatoid mRCC [185].

Chemotherapy combined with sorafenib has demonstrated significant efficacy in the first-line setting of mRCC for collecting tube RCC. Also, ICI plus axitinib showed good antitumor effect and deserves further study [64].

Thus, widespread introduction of ICI group drugs into the practice of mRCC treatment has led to an increase in the effectiveness of therapy of non-small cell variants of mRCC.

1.8.2.5 Features and prospects of systemic therapy metastatic renal cell cancer in the first line

According to current NCCN guidelines (version 1.2020), first-line therapy for mRCC included sunitinib, pazopanib, cabozantinib, TKI, or TKI combined with axitinib [20, 47, 107, 159]. In a 2000-2020 survival analysis of mRCC patients, the median OS was 13 months with first-line IFN-a treatment, 19 months when patients started treatment with TKI, and 45 months when first-line treatment was ICI-based ($p<0.0001$). This difference remained significant even after adjustment for known prognostic factors (IMDC risk groups, baseline CRP levels, presence of bone or brain metastases). Five-year OS was 7%, 21%, and 36% in patients receiving first-line IFN-a, TKI, and ICI, respectively [179].

In the first-line setting, combination therapy with axitinib with pembrolizumab antibody or avelumab was used regardless of risk profile and histologic variant, as was the combination of ipilimumab with nivolumab in patients with intermediate and poor prognosis according to IMDC as new standards of therapy. During a median follow-up of 23.0 months, the median OS was 24.3 months with ICI-based combinations and 14.8 months with TKI monotherapy, and the median PFS was

9.3 and 3.4 months, respectively. Objective response was observed in 60% of patients receiving ICI-based combinations and 19% of patients receiving TKI monotherapy. In a multivariate regression model, the number of IMDC risk factors and ICI-based combination therapy were independent prognostic factors for PFS [30]. Phase III trials of first-line ICI combinations also showed survival advantages compared to sunitinib-treated controls: median OS 47.0 vs. 26.6 months, median PFS 11.6 vs. 8.3 months in patients with intermediate and poor prognosis. The OS was also significantly increased with the use of ICI combinations [101].

CheckMate 214 was the first randomized phase III trial to demonstrate the clinical activity of ICI combination therapy in patients with intermediate or poor prognosis according to the IMDC scale [165]. This study compared the combination of ipilimumab and nivolumab versus sunitinib. The PFS was 42% vs. 27% (9% vs. 1% complete response (CR)) in favor of the combination compared to sunitinib. The median OR was still not reached after 30 months for the combination [268], and it appeared that increased PFS was observed in the TKI-treated population as well as in the intermediate/favorable prognosis population [268]. Sunitinib showed higher complete response rate (CRR) (29% vs. 52%) and PFS (15.3 vs. 25.1 months) in patients from the favorable prognosis group compared to combination therapy, and this superiority continued, although the gap narrowed after 30 months of follow-up with CRR of 39% vs. 50% and PFS of 13.9 vs. 19.9 months. At the last 42-month follow-up [178], median PFS remained high for both patients receiving the combination and those receiving ICI, as well as in the intermediate/favorable prognosis population. The PFS of the combination continued to be higher in the ipilimumab+nivolumab cohort (PFS 42%, including 10% CR). The PFS was 0.76, and 35% of patients did not experience progression with the ipilimumab+nivolumab combination, compared with 13% of patients in the sunitinib group. Among patients with a favorable prognosis, the PFS continued to be higher with sunitinib after 42 months of follow-up (54% vs. 29%); however, more patients achieved complete remission with the ipilimumab+nivolumab combination (13% vs. 6%). Responses to combination therapy were more robust than to sunitinib in all IMDC prognosis

groups, and the likelihood of PFS stabilized with the combination and decreased with sunitinib in patients in the favorable prognosis group. This 42-month follow-up was the longest among all phase III trials of combination immunotherapy as first-line therapy for mRCC [178].

1.8.2.6 Features and prospects of systemic therapy metastatic renal cell cancer in the second line

Changing first-line therapy inevitably led to modification of the entire algorithm of mRCC treatment; to date, the most appropriate second-line options remain unclear. Data on drug safety and activity induced a shift to single-agent systemic therapy in the second-line setting. Nivolumab monotherapy has clinical justification as a second-line therapeutic option for patients who have received targeted therapy in the first-line setting [228]. Retrospectively, the efficacy of second-line TKI appears to be higher after failure of dual ICI combination than after ICI plus TKI combination; however, prospective data on the use of second-line TKI are limited. Moreover, repeated ICI may be considered as an option, but again, most data are from retrospective studies emphasizing the identification of prognostic response factors to select patients with mRCC who could benefit from this strategy. For second-line therapy, cabozantinib was identified as the most effective treatment option when evaluated for PFS. Axitinib had the lowest incidence of adverse events and drug withdrawal. Pazopanib was the second drug of choice in terms of AEs compared to placebo [24].

After progression on first-line TKI therapy, three new therapies have recently been approved as second-line options that further expand the treatment armamentarium: nivolumab; cabozantinib; and lenvatinib, which is used in combination with everolimus [250], with the latter combination considered to be the most effective with respect to survival rates [247]. Retrospectively studying patients

with clear cell mRCC receiving second-line TKI after disease progression on ICI therapy as first-line therapy, the following data were obtained: on second-line TKI therapy, one patient (1.5%) achieved a complete response, 27 patients (39.7%) achieved a partial response, and 36 patients (52.9%) had disease stabilization. The median PFS was 13.2 months. 45% of patients required dose reduction and 27% of patients discontinued treatment due to toxicity. Thus, the antitumor activity and tolerability of second-line TKI appeared comparable to historical data for first-line TKI [147].

Nivolumab and cabozantinib improved survival compared to everolimus in the second-line treatment of mRCC. Lenvatinib plus everolimus similarly demonstrated encouraging survival benefits in a phase II study in second-line patients. New combinations for mRCC, including ICI combination, TKI and vaccine therapy, dual angiogenic blockade, and nanoparticle-containing camptothecin therapy, have shown promising activity in early-stage trials [37].

New molecules and various combinations are under investigation and evaluation. In particular, belzutifan, siforadenant (CPI-444) and talazoparib have shown encouraging rates of CRR in phase I/II studies. Phase III trials comparing these new molecules to standard of care are ongoing. The first-line regimen as well as the type and duration of response have been shown to be crucial factors that could influence the efficacy of second-line therapy [75].

1.8.2.7 Features and prospects of systemic therapy metastatic renal cell cancer in the third and subsequent lines

Second- or third-line treatment options for mRCC have evolved dramatically over the past few years, but the number of studies evaluating the efficacy and safety of third- and subsequent-line therapy is limited. Data on 48 patients with progression of mRCC after second-line TKI were evaluated. Patients with third-line therapy had

significantly longer median OS after first-line therapy (26.6 vs. 14.6 months) and second-line therapy (18.2 vs. 7.4 months) compared with patients without third-line therapy. Multivariate analysis showed that the use of third-line therapy after second-line therapy was an independent prognostic factor for longer OS. The median PFS and OS after third-line therapy were 2.76 and 8.71 months, respectively, indicating that third-line therapy had a favorable therapeutic effect in patients with mRCC resistant to previous therapies. However, there was a need for detailed evaluation of the high incidence of adverse events, including toxicity [93]. In first-, second-, and third-line therapy, approximately 20% of patients experienced prolonged PFS >15 months. With targeted treatment beyond third-line therapy, disease progression was delayed beyond 10 months. Among patients who died during the follow-up period and received 3rd and 4th line treatment, similar rates of OS were observed (42.5 vs. 48.4 months, respectively). Multivariate analysis showed that patients with three or more lines of therapy had better OS; however, 4 or more lines of therapy had no prognostic value. Consequently, third-line systemic therapy may improve OS; however, fourth-line therapy had no such effect [91]. A German study showed that only 6.16% of the original cohort of mRCC patients received 5-line therapy, and the disease control rate with fifth-line therapy was 20%. The median OS from initiation of first-line therapy was 50.2 months, and the median OS from initiation of fifth-line therapy was 6.2 months. The median PFS for fifth-line systemic therapy was 4.1 months and did not correlate with response to first-line treatment with targeted agents. Thus, carefully selected patients may benefit from fifth-line treatment regardless of treatment response to first-line targeted therapy [221].

According to the data of I. Stukalin et al., everolimus was the most frequently used drug in 4 lines (16.8%). Sorafenib, axitinib, pazopanib, sunitinib and clinical trial drugs were also used in more than 10% of patients. The median OS was 12.8 months with a PFS of 4.4 months, and the PFS was 13.7%. IMDC prognosis had a significant impact on OS, while age >70 years and non-small cell variant had no effect on OS [110].

In the Checkmate 025 trial, 821 patients with mRCC who had previously received one or two lines of TKI were randomized 1:1 to compare the efficacy of nivolumab or everolimus. Treatment after progression was allowed if clinical benefit was observed and the drug was well tolerated. The median OS for nivolumab was 25 months and for everolimus was 19.6 months. The benefit in OS was observed regardless of PD-L1 expression. Nivolumab also increased the CRR to 25% compared to 5% for everolimus, but the PFS did not differ between groups. The median PFS was 4.6 months in the nivolumab group and 4.4 months in the everolimus group. A follow-up analysis of those who did not progress at 6 months recommended the use of nivolumab [166]. In a study of 687 patients, the PFS for second-line, third-line, and fourth-line nivolumab was 22%, 24%, and 26%, respectively. The median treatment duration was 5.7, 6.2, and 8.3 months, respectively. When divided into IMDC groups, median OS for first-line, second-line, third-line, and fourth-line treatment were not achieved. Thus, the overall response rate did not decrease from first-line to fourth-line TKI therapy [57]. Studying different TKI-nivolumab-cabozantinib or TKI-cabozantinib-nivolumab sequences, the median OS and PFS for third-line treatment were 27 and 5.2 months for nivolumab, 16.6 and 7.5 months for cabozantinib. The median OS for the nivolumab-cabozantinib sequence compared with the cabozantinib-nivolumab combination was 28.8 versus 19.9 months; the median PFS for both sequences was similar at 5.7 months, recognizing both combinations as effective strategies in terms of OS and cost-effectiveness [215].

Sunitinib has occasionally been used as a third-line treatment in selected mRCC patients, and its use has not demonstrated significant differences in OS, PFS, and disease control compared with first- and second-line treatment [174].

Thus, the data on the results of systemic therapy for mRCC demonstrated the undoubted efficacy of ICI associated with an increase in the duration of OS and PFS, which did not decrease in subsequent lines of therapy. However, publications on the third and subsequent lines of therapy for mRCC are extremely scarce.

Conclusion

Over the past 15 years, unprecedented progress has been made in the treatment of mRCC, resulting in significant improvements in patient prognosis. The two major classes of agents used in the current treatment paradigm are TKI and ICI. Further study will focus on the use of these agents based not only on clinical characteristics but also on molecular profiling. The prolongation of OS and PFS rates requires an increase in the number of lines of systemic therapy and the study of their combinations, and the development of new prognostic scales and predICIors of survival. Although the available studies to date have focused on the results of combinations and monotherapy of drugs mainly in the 1st and 2nd lines. In the context of personalized treatment of mRCC, clinical trials are currently investigating new systemic drugs, developing approaches to individualize current combination therapy, and identifying promising biomarkers as tools for appropriate patient selection.

Continued advances in knowledge of molecular biology, cancer genetics, and the interactions between tumors and the immune system are rapidly changing our understanding of cancer, altering our approach to diagnosing and treating the disease. This progress is particularly important in mRCC, as the combination of ICI with targeted agents has become standard practice and many recent clinical trials have demonstrated the efficacy of therapy in a significant proportion of patients. The biggest challenge that clinicians are likely to face in the near future is to use these agents and their combinations in an individualized approach that will provide the optimal balance of efficacy/toxicity and maximize cost-effectiveness.

In summary, the treatment modalities for mRCC have undergone significant changes in recent years, resulting in increased overall survival.

A multifactorial analysis of the patient is important, including clinical and laboratory, pathomorphological characteristics of the tumor, the number of affected organs, the time of occurrence and localization of metastases. When prescribing systemic therapy, preference should be given to drugs analyzing these initial characteristics of the patient.

Chapter 2
MATERIAL AND RESEARCH METHODS

2.1 General characteristics of patients

We retrospectively analyzed the database of 981 patients with mRCC who received systemic therapy at the Municipal Oncology Hospital No. 62 in Moscow and the Municipal Oncology Dispensary in St. Petersburg from 2006 to 2022. Of 981 patients, 877 patients received only targeted therapy, and 104 patients were additionally treated with immunotherapy with immune checkpoint inhibitors. For this group of patients, we had all necessary individual clinical and laboratory data as well as information on overall life expectancy. All patients were dynamically monitored throughout the treatment. When analyzing the frequency of objective effects, time to progression, OS, and factors affecting these parameters, we combined all 981 patients into a single group, since all patients received different variants of systemic therapy. All patients included in this analysis had morphological verification of RCC diagnosis, distant or regional metastases, and no severe concomitant pathology preventing systemic therapy (uncontrolled forms of arterial hypertension, unstable angina, acute myocardial infarctions and strokes).

All patients underwent a standard set of diagnostic measures, including general clinical, biochemical blood tests, coagulogram, urinalysis, ECG, EGDS, ECHO-CG, ultrasound of the abdominal cavity, retroperitoneum and small pelvis, bone scanning, as well as CT of the lungs and abdominal cavity.

The main inclusion criteria for patients with mRCC in the study were:

- over 18 years of age;
- a history of nephrectomy, resection or biopsy of the kidney;
- morphologic confirmation of renal cell carcinoma;
- the absence of a primary-multiple process;

- presence of kidney cancer metastases confirmed by objective methods of investigation (CT, ultrasound, MRI, osteoscintigraphy, PET-CT).

Figure 2.1 shows that our study was male dominated with 704 patients (71.8%) and female patients were 277 (28.2%).

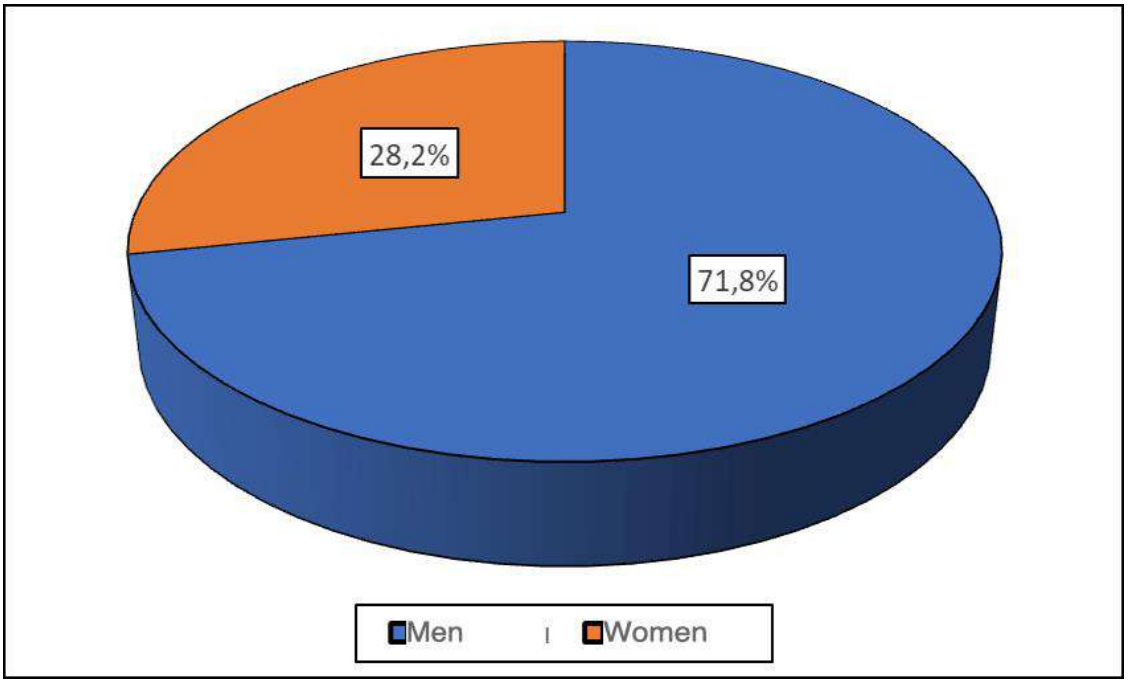


Figure 2.1 – Distribution of patients by gender

The mean age of the patients was 60.8±9.7 years, the youngest was 22 years old, the oldest was 95 years old, 95% CI was 60.2÷61.4 years. The modal index was age equal to 63 years, median – 61 years, interquartile range – from 54 to 67 years.

As shown in Figure 2.2, left kidney tumor was detected in 482 (49.1%) patients, right – 475 (48.4%) patients, bilateral lesion was diagnosed in 24 (2.5%) patients.

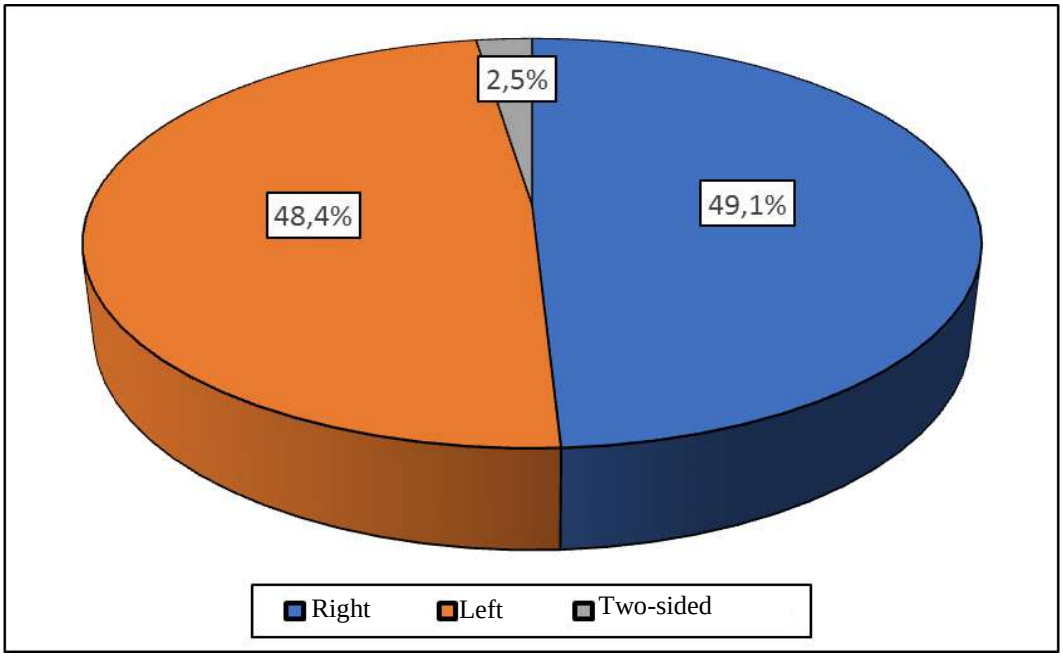


Figure 2.2 – Distribution of patients by side of the lesion

Table 2.1 shows that the most common nephrectomies performed in mRCC patients were right and left nephrectomies in 423 (43.1%) and 446 (45.5%) patients, respectively.

Table 2.1 – Distribution of patients by types of surgical treatment of primary kidney tumor

View surgical treatment	Number of patients 981	Percentage (%) 100
Nephrectomy on the right	423	43.1
Nephrectomy on the left	446	45.5
Right renal resection	18	1.8
Left renal resection	14	1.4
Kidney tumor biopsy	80	8.2

In 901 (91.8%) patients, the primary renal neoplasm was removed at various time points prior to systemic therapy.

Group 1 – 578 (58.9%) patients with metachronous metastases of RCC who underwent surgery on the primary tumor, of which 571 (98.8%) patients underwent radical kidney surgery, 7 (1.2%) were not operated on for various reasons.

Group 2 – 403 (41.1%) patients with synchronous metastases of RCC initially with metastatic stage, who underwent cytoreductive surgery with/without metastasectomy, of whom 330 (81.9%) patients underwent cytoreductive nephrectomy/renal resection. Of them – 62 patients underwent cytoreductive surgery + metastasectomy, 268 patients underwent cytoreductive surgery without metastasectomy. 73 (18.1%) patients underwent diagnostic biopsy of renal tumor.

Cytoreductive surgeries in mRCC patients were performed in combination with systemic drug therapy.

In the study, in 226 (70%) patients, retroperitoneal lymphadenectomy was most commonly performed in terms of combined operations (Figure 2.3).

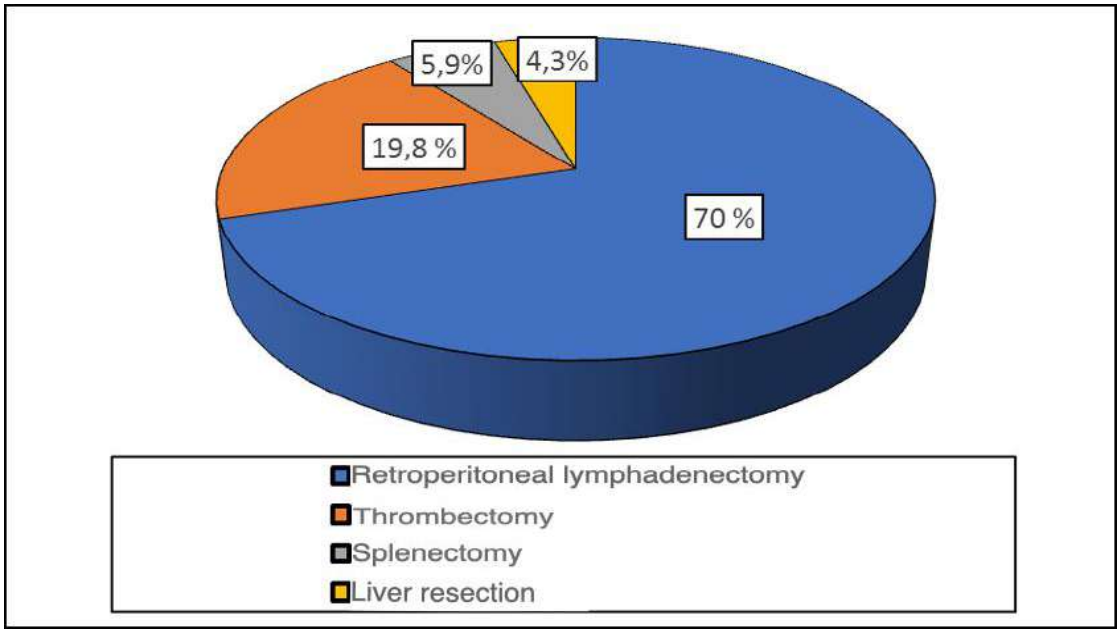


Figure 2.3 – Distribution of patients by types of combined operations

Pathomorphological evaluation of the tumor after surgery or biopsy was performed in all patients according to the results of histological studies. The

distribution of cases by histological variants of RCC is presented in Figure 2.4. In the majority of patients 867 (88.3%) renal cell luminal cancer prevailed.

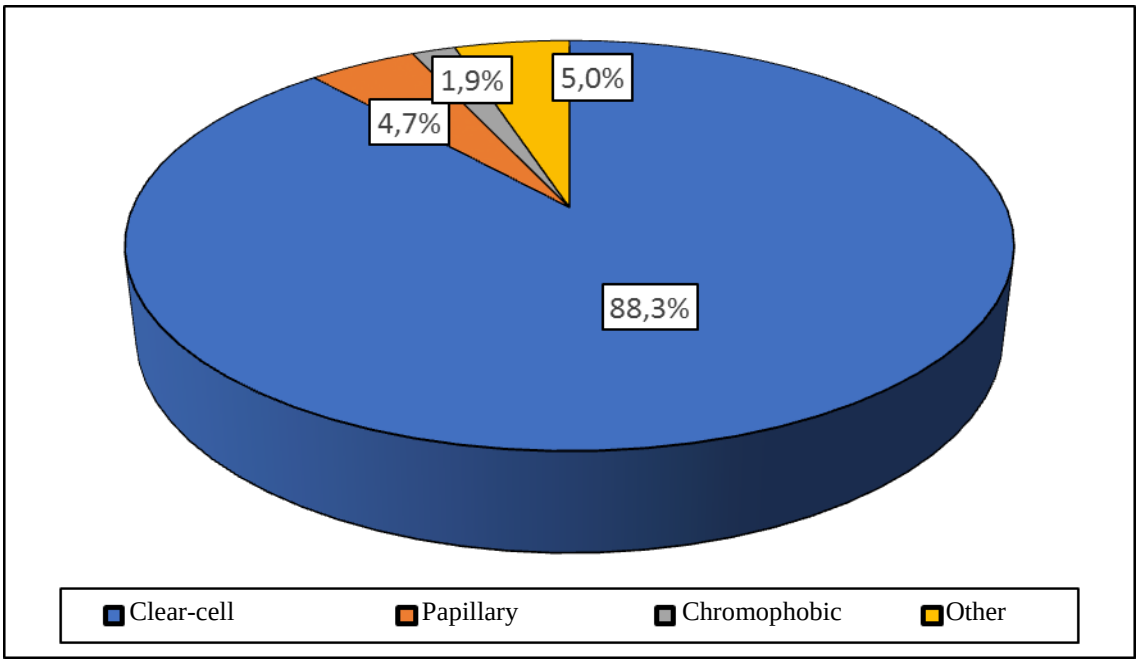


Figure 2.4 – Distribution by RCC variants

Depending on the tumor differentiation according to Fuhrman, the patients were distributed as follows:

- G1 – 186 (19%);
- G2 – 360 (36.7%);
- G3 – 435 (44.3%).

The majority of patients were found to have moderately and low-differentiated tumors (81%).

The general medical status of mRCC patients was determined using the ECOG-WHO scale, which includes an assessment of mRCC patients' activity in scores from 0 to 3.

According to ECOG status, the patients were distributed as follows, Table 2.2:

Table 2.2 – Distribution of patients depending on ECOG status

ECOG status	Number of patients 981	Percentage (%) 100
0	57	5.8
1	399	40.7
2	347	35.4
3	178	18.2

The majority of patients had ECOG1 status 2 (76.1%).

Distribution by IMDC forecast groups

According to the recommendations, before treatment, patients were divided into favorable, intermediate, and unfavorable prognosis groups depending on the number of characteristics present. To evaluate the prognosis of previously untreated patients undergoing targeted therapy, the IMDC (International Metastatic Renal Cell Carcinoma Database Consortium) prognostic model is used in clinical practice [32], which included the following characteristics for evaluation:

1. Time from diagnosis to initiation of treatment is less than 1 year.
2. Hemoglobin level is below the lower limit of normal (less than 110 g/L).
3. Somatic status on the Karnofsky scale is less than 80%.
4. Adjusted serum calcium concentration is above the upper limit of normal (greater than 2.5 mmol/L).
5. Neutrophil levels are above the upper limit of normal.
6. Platelet count is above the upper limit of normal.

In mRCC patients of the favorable prognosis group these unfavorable factors were absent, in the intermediate prognosis group there were no more than 2 factors, and in the unfavorable prognosis group – 3 or more negative factors (Figure 2.5).

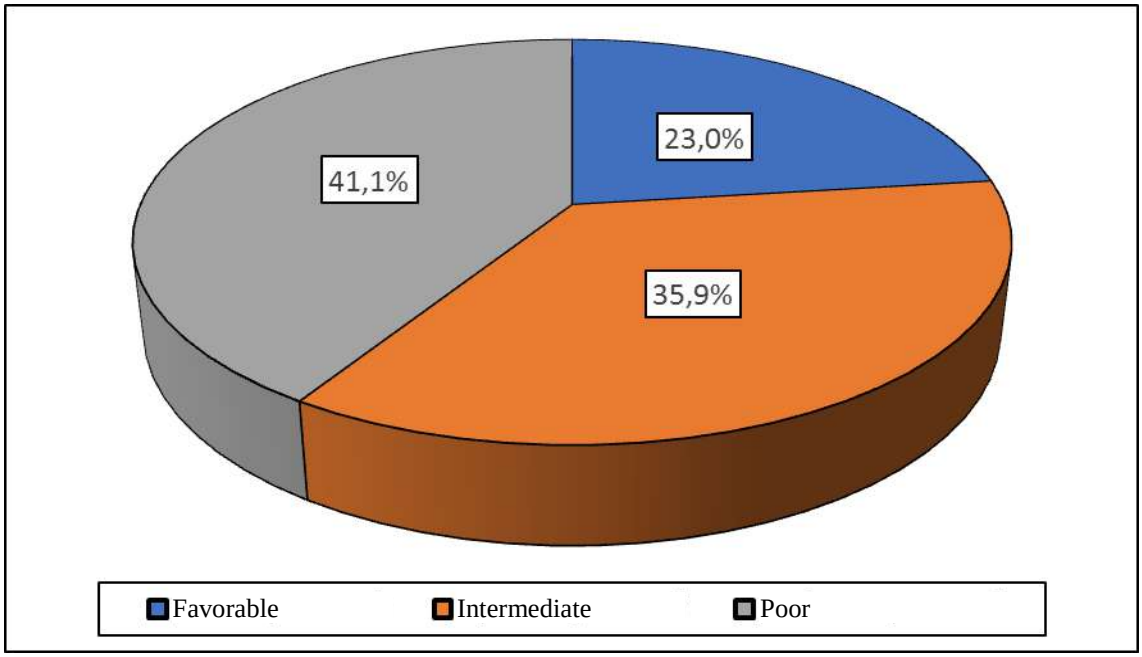


Figure 2.5 – Distribution of mRCC patients
depending on the IMDC forecast

Table 2.3 shows that the most frequent metastases to lung, bone and lymph nodes were detected in mRCC patients in 655 (66.7%), 380 (38.7%) and 334 (34.0%) respectively.

Table 2.3 – Distribution of patients by localization of metastases

Localization of metastases	Number of patients 981	Percentage (%) 100
Lungs	655	66.7
Bones	380	38.7
Lymph nodes	334	34.0
Liver	141	14.4
Adrenal gland	122	12.4
Kidney	73	7.4
Brain	56	5.7
Others (soft tissue, spleen, ovary, uterus, pancreas, and thyroid).	199	20.3

Surgical treatment of metastases was performed in 294 (30%) patients. Lung resection or lobectomy – 64 (6.5%), resection of femur, iliac, humerus or ribs – 32 (3.4%), endoprosthesis or osteosynthesis of bones – 26 (2.6%), vertebroplasty – 24 (2.4%), removal of recurrence in the kidney bed and laminectomy – 23 (2.3%), respectively (Table 2.4).

Table 2.4 – Nature of palliative surgical treatment

Types of operations	N (%) 294 (30%)
Lung resection or lobectomy.	64 (6.5%)
Resection of femur, iliac, humerus or ribs	32 (3.3%)
Endoprosthetics or bone osteosynthesis	26 (2.6%)
Vertebroplasty	24 (2.4%)
Removal of a recurrence in the kidney bed	23 (2.3%)
Laminectomy	23 (2.3%)
Removal of mts in the brain or spinal cord	18 (1.8%)
Adrenalectomy	12 (1.2%)
Liver resection	10 (1%)
Transperitoneal lymphadenectomy.	9 (0.9%)
Splenectomy	9 (0.9%)
Hemicolectomy or intestinal resection	7 (0.7%)
Removal of mts of the skin or p/k fiber	6 (0.6%)
Bone amputation (extirpation)	8 (0.8%)
Kidney resection	6 (0.6%)
Pancreatic resection	7 (0.7%)
RFA (liver, kidney)	6 (0.6%)
Pancreaticoduodenal resection	3 (0.3%)
Thyroidectomy	2 (0.2%)
Adnexectomy	1 (0.1%)
Cryoablation of the liver	1 (0.1%)
Uterine extirpation	1 (0.1%)
Thrombectomy	1 (0.1%)

The long-term outcomes of the study were defined as OS and PFS, 3-year, 5-year, and 10-year survival rates. In all groups of patients, OS was defined as the period from the appearance of distant metastases to the date of death or the date of the last examination for censored patients (in months).

The immediate outcomes of the study were to determine the frequency of objective responses and prognostic factors.

The frequency of objective effects was assessed according to RECIST criteria (Response Evaluation Criteria In Solid Tumors, 2000):

1. Complete response is the disappearance of all control and non-control foci, determined twice, no earlier than four weeks after compliance with response criteria was first detected.

2. Partial response – reduction of the sum of the largest diameters of the control foci by at least 30% compared to the initial sum. Absence of appearance of new foci.

3. Stabilization – no decrease in the size of foci, which could be regarded as a partial response, or increase in the size of foci, which could be regarded as disease progression (compared to the minimum value recorded when determining the sum of the largest diameters since the start of treatment). No appearance of new foci.

4. Progression – increase in the sum of the largest diameters of the control foci by at least 20% compared to the minimum value recorded when determining the sum of the largest diameters since the start of treatment, or the appearance of one or more new foci.

Nonparametric data, depending on the number of observations, were analyzed using theχ^2 test or Fisher's exact test. In all cases, 95% confidence interval and two-sided p were used.

The PFS for all patients included in the study was determined from the date of treatment initiation for metastatic stage to the date of progression on line of therapy or the date of last follow-up.

Drug doses were calculated taking into account the recommendations of the European Society of Clinical Oncologists (ESMO) and the Russian Society of Clinical Oncologists (RUSSCO).

The toxicity of the treatment was assessed according to the internationally accepted common criteria for determining the type and degree of toxicity (Common Toxicity Criteria, version 3).

The efficacy of mRCC treatment was evaluated in all 6 lines. The criterion for switching to the next line of mRCC therapy was disease progression according to RECIST criteria on the current treatment or withdrawal from different treatment regimens due to toxicity.

Thus, of 981 patients, 667 (68%) received 2 lines and 558 patients received three or more lines of systemic therapy.

The distribution of drugs by line is presented in Table 2.5.

Table 2.5 – Systemic therapy in mRCC patients

Drugs	1 line N (%)	2 lines N (%)	3 lines or more N (%)
	(N=981)	(N=667)	(N=558)
Nexavar	283 (28.8)	167 (25)	73 (13.1)
Sutent	221 (22.6)	228 (34.2)	111 (19.9)
Pazopanib	160 (16.3)	102 (15.2)	118 (21.2)
Avastin	61 (6.2)	27 (4.0)	28 (5)
Cytokine immunotherapy	169 (17.2)	11 (1.7)	9 (1.6)
Axitinib	10 (1.1)	11 (1.7)	33 (5.9)
Tivozanib	3 (0.3)	1 (0.1)	–
Chemotherapy	5 (0.5)	13 (1.9)	6 (1)
Temsirolimus	25 (2.1)	5 (0.8)	9 (1.6)
Everolimus	9 (0.9)	51 (7.6)	115 (20.7)

Continuation of Table 2.5

Drugs	1 line N (%)	2 lines N (%)	3 lines or more N (%)
Cabazantinib Lenvatinib+Everolimus Immunotherapy with checkpoint inhibitors	1 (0.1) – 34 (3.5)	7 (1.0) 7 (1.0) 37 (5.5)	9 (1.6) 13 (2.3) 34 (6.1)
Duration, months.	13.4 (median 1-107)	13.3 (median 1-104)	11.0 (median 1-83)

2.2 Dosages and regimens of systemic therapy drugs

1. Antiangiogenic drugs

Monoclonal antibodies (antibodies to VEGF)

Bevacizumab is a humanized antibody that binds VEGF-A isoforms. The dose of bevacizumab is 10 mg/kg w/v drip once every 2 weeks. The drug is administered in combination with IFN-α with gradual escalation of the dose of the latter from 3 million units 3 times a week subcutaneously during the 1st week of therapy, to 6 million units 3 times a week subcutaneously during the 2nd week of therapy and to 9 million units 3 times a week subcutaneously during the 3rd and subsequent weeks of therapy. If IFN-α is poorly tolerated, the single dose may be reduced to 6 million IU or 3 million IU. b. Protein kinase inhibitors (multikinase inhibitors).

Sorafenib is an oral multikinase inhibitor that inhibits the activity of serine-threonine kinase Raf-1, B-Raf, VEGF type 2 receptor (VEGFR2) and PDGF receptor (PDGFR), FMS-like tyrosine kinase-3 and c-KIT. The drug is administered in mono-regimen, 51 daily dose is 800 mg (4 tablets of 200 mg). It is prescribed in 2 doses (2 tablets 2 times a day). If necessary, the dose of the drug can be reduced to 400 mg once a day or to 400 mg every other day.

Sunitinib is an oral multikinase inhibitor of growth factors PDGFR, VEGFR, c-KIT and FMS-like tyrosine kinase 3 with antitumor and antiangiogenic activity. The drug is administered in mono-regimen, its dose is 50 mg/day for 4 weeks followed by a break for 2 weeks (4/2 regimen). The full cycle of therapy is 6 weeks. If necessary, the dose of the drug can be reduced by 12.5 mg, up to 37.5 mg/day. In patients with poor individual tolerance to the 4/2 regimen, sunitinib can be administered at a dose of 50 mg/day for 2 weeks followed by a break for 1 week (regimen 2/1).

Pazopanib is an oral selective inhibitor of tyrosine kinases, VEGFR, PDGFR and c-KIT. The drug is administered in mono-regimen, its dose is 800 mg once a day. If necessary, the daily dose of the drug can be reduced or increased in 200 mg increments, with the maximum daily dose not to exceed 800 mg and the minimum daily dose not to be lower than 400 mg.

Axitinib is an oral high-affinity tyrosine kinase inhibitor that blocks VEGFR1-3. The drug is administered in mono-regimen or in combination with PD(L)-1 inhibitors (pembrolizumab 200 mg once every 3 weeks or 400 mg once every 6 weeks or avelumab 10 mg/kg or 800 mg once every 2 weeks). Both when prescribing axitinib monotherapy and when using combinations based on this drug, the initial dose of axitinib is 5 mg 2 times a day with an interval between doses of 12 h. In patients who tolerate the drug in the initial dose (5 mg twice a day) without development of adverse events (AEs) above II degree of severity according to the Common Terminology Criteria for Adverse Events (CTCAE) for 2 consecutive weeks, provided that blood pressure does not exceed 150/90 mmHg and there is no need for standard hypotensive therapy, it is possible to increase the dose up to 7 mg twice a day. Then using the same criteria for patients tolerating axitinib at a dose of 7 mg 2 times a day, it is possible to further increase the dose of the drug up to the maximum dose of 10 mg 2 times a day. If necessary, it is allowed to reduce the dose of axitinib to 3 mg 2 times a day, then – to 2 mg 2 times a day.

Lenvatinib is an oral multikinase inhibitor of FGFR1-4, VEGFR1-3, PDGFR-α, as well as RET and KIT receptors. The daily dose of lenvatinib depends on the composition of the combination administered. In combination with everolimus

5 mg/day the daily dose of lenvatinib is 18 mg (1 capsule 10 mg and 2 capsules 4 mg) once a day. If necessary, the daily dose of the drug can be reduced or increased in 4 mg increments, with the maximum daily dose not exceeding 18 mg and the minimum daily dose not below 10 mg. In combination with pembrolizumab 200 mg once every 3 weeks or 400 mg once every 6 weeks, the daily dose of lenvatinib is 20 mg (2 10 mg capsules) once daily. If necessary, the daily dose of the drug can be reduced or increased in 4 mg increments, with the maximum daily dose not exceeding 20 mg and the minimum daily dose not below 10 mg.

Cabozantinib is an oral multikinase inhibitor of VEGFR1-3, AXL, MET (hepatocyte growth factor receptor), as well as RET, stem cell growth factor receptors KIT, FLT3, ROS1, MER, TYRO3, TRKB and TIE-2. When prescribing cabozantinib monotherapy, the daily dose is 60 mg once a day. If necessary, the dose of the drug can be decreased or increased in increments of 20 mg, with the maximum daily dose not exceeding 60 mg and the minimum daily dose not being below 20 mg. When administered in combination with nivolumab 240 mg once every 2 weeks or 480 mg once every 4 weeks, the daily dose of cabozantinib is 40 mg once a day. If necessary, the drug dose can be reduced to 20 mg.

2. Selective immunosuppressants that inhibit mTOR

Everolimus is an oral mTOR inhibitor that blocks the TORC-1 protein complex. The drug is administered both in monotherapy and in combination with lenvatinib. The recommended dose for monotherapy is 10 mg once a day. If necessary, the dose of the drug can be reduced to 5 mg/day. In combination with lenvatinib everolimus is administered at a dose of 5 mg/day. Dose reduction is not envisaged.

Temsirolimus is an mTOR inhibitor that blocks the TORC-1 protein complex. The dose of temsirolimus is 25 mg w/v drip over 30-60 min once a week. If necessary, the drug dose can be reduced by 5 mg per week.

3. Immunomodulators

Immunostimulants: interferons

Interferon-alpha is a pro-inflammatory cytokine, administered in combination with bevacizumab. IFN-α is administered at a starting dose of 3 million units 3 times a week subcutaneously during the 1st week of therapy. In the absence of severe NHL, the dose is increased to 6 million units 3 times a week subcutaneously during the 2nd week of therapy and up to 9 million units 3 times a week subcutaneously during the 3rd and subsequent weeks of therapy. In case of poor tolerance of IFN-α, the single dose of the drug can be reduced to 6 million units or 3 million units.

4. PD-1 inhibitors

Nivolumab is a monoclonal antibody to PD-1. The drug can be administered in monotherapy or in combinations with ipilimumab or cabozantinib. As monotherapy, nivolumab is administered at a dose of 3 mg/kg or 240 mg every 2 weeks or 480 mg every 4 weeks intravenously as a 30-minute or 60-minute infusion. In combination with ipilimumab, nivolumab is administered at a dose of 3 mg/kg followed by ipilimumab at a dose of 1 mg/kg on the same day as a 30-minute IV infusion, every 3 weeks, for a total of 4 administrations. This is followed by nivolumab monotherapy at a dose of 3 mg/kg or 240 mg – 1st infusion 3 weeks after the last co-infusion, then every 2 weeks, or at a dose of 480 mg – 1st infusion 6 weeks after the last co-infusion, then every 4 weeks. In combination with cabozantinib 40 mg/day, nivolumab is administered at a dose of 240 mg every 2 weeks or 480 mg every 4 weeks by IV drip. There is no dose reduction of nivolumab.

Pembrolizumab is a monoclonal antibody to PD-1. The drug can be used in combinations with axitinib (5 mg twice daily) or lenvatinib (20 mg/day). Pembrolizumab is administered at a dose of 200 mg w/v drip once every 3 weeks or 400 mg once every 6 weeks. There is no dose reduction of pembrolizumab.

5. PD-L1 inhibitors

Avelumab is a human immunoglobulin G1 (IgGl) monoclonal antibody directed against PD-L1. The drug is administered at a dose of 10 mg/kg or 800 mg w/v drip over 1 h once every 2 weeks or at an equivalent dosage according to the

instructions for use in combination with axitinib 5 mg twice daily orally. Dose reduction of avelumab is not foreseen.

6. CTLA-4 inhibitors

Ipilimumab is a monoclonal body to CTLA-4. The recommended dose of ipilimumab is 1 mg/kg v/v drip once every 3 weeks, 4 injections. It is administered in combination with nivolumab at a dose of 3 mg/kg or 240 mg once every 3 weeks by IV drip, 4 injections. Followed by nivolumab monotherapy at a dose of 3 mg/kg or 240 mg once every 2 weeks or 480 mg once every 4 weeks by IV drip. There is no dose reduction of ipilimumab.

2.3 Research Methods

In order to determine the prevalence of the tumor process, the complex of examination of each patient included:

1. Examination of the patient by organs and systems.
2. Study of anamnestic data, medical records.
3. Radiography and computed tomography (CT) of the chest organs.
4. Ultrasound (ultrasound), CT of abdominal, retroperitoneal and pelvic organs with intravenous contrast.
5. Radioisotope examination of the skeleton (osteoscintigraphy).
6. Bone radiographs.
7. MRI/CT of the brain.
8. Laboratory tests: complete blood count, blood chemistry, urinalysis, tumor markers, bone resorption markers, etc.
9. Morphologic examination of the removed material.

Radiologic examination of bones was performed on X-ray diagnostic remote-controlled rotary tables Axiom Iconos R 200 (Siemens, Germany) and Prestige-SI (General Electric, USA).

Ultrasound examination of the abdominal cavity organs was performed on expert-level devices "Aplio MX", "Aplio 500" (Toshiba Medical System, Japan) and "MyLab Twice" (Esaote, Italy) using wide-band transducers with a basic frequency of 3.5 MHz.

Multispiral CT of the chest, abdomen, and pelvis was performed on Aquilion Prime and Aquilion 64 CFX (Toshiba Medical System, Japan) with bolus contrast enhancement. MISSISSIPPI injector (Ulrich Medical GmbH, Germany) was used for intravenous injection of radiographic contrast agent.

MRI was performed in patients to clarify the spread of the tumor process. The studies were performed on the Excelant Vantage Atlas ZGV device with a magnetic field of 1.5T and a magnetic field strength change rate of 200 mT/m/ms (Toshiba Medical System, Japan). T1- and T2-weighted images, diffusion-weighted images were analyzed.

Laboratory studies: complete blood count, biochemical blood count, urinalysis, tumor markers, bone resorption markers were performed in the clinical diagnostic laboratory on a Siemens-315 and Cobas C111 blood analyzer according to the standard mode. The results of blood tests were calculated in standard units of measurement.

2.4 Creating mathematical models to predict survival rates and outcomes of patients with metastatic renal cell cancer

2.4.1 Logistic regression model for forecasting indicators 5-year overall survival rate and its estimation using the ROC analysis

The method of logistic regression was chosen as a mathematical and statistical method of solving the problem, the main condition for the use of which is the

dichotomous nature of the predicted trait, as well as qualitative predominantly dichotomous trait predictors.

2.4.2 Creation of a modified predictive model in patients with metastatic Renal cell cancer based on the factors identified in the study

Cox multivariate analysis was performed to determine statistically significant prognostic factors affecting survival rates in mRCC patients. A modified SOSh prognosis model (Semenov, Orlova, Shirokorad) was created for mRCC patients based on 8 significant prognostic factors, including the type and number of metastases, the degree of tumor differentiation according to Fuhrman, hemoglobin level, ECOG status, CN and metastasectomy, presence or absence of visceral metastases.

2.5 Statistical processing of data

Statistical support of the study was carried out with consistent use of diverse and adequate mathematical and statistical methods. Input, accumulation, storage and primary sorting of the study data were carried out using PC and Excel. Mathematical and statistical processing of the study data was carried out using Excel tabular editor, in particular, its modules "Data Analysis" and "Chart Wizard" and Statistica for Windows statistical software package. The results of statistical processing are presented in tabular and graphical form.

Quantitative indicators were checked for conformity of their distribution to the normal or close to it distribution law using the Shapiro-Wilk criterion. If the normal distribution was confirmed, parametric statistics methods were used to describe the

signs and calculated: arithmetic mean (M), variability was assessed using the mean square deviation (δ), the standard error of mean (m) and 95% confidence intervals (95% CI) were used to extrapolate the study data. The significance of the difference between the indicators was assessed using Student's t-criterion for two independent or pairwise related samples. The relationship between the signs was assessed using the parametric Pearson's r correlation coefficient.

When the distribution of a trait was different from the normal law, it was described by the median (Me), maximum and minimum values (Xmin, Xmax), quartile values (Q25÷Q75) and interquartile range (Q75-Q25). The significance of the difference between independent samples was assessed using the nonparametric Mann-Whitney criterion; when comparing several unrelated samples, the Kraskell-Wallis method was used. The correlation between two indicators using the Spearman correlation coefficient.

Qualitative indicators were described using relative values of frequency and distribution. Differences in relative frequency values were evaluated using Student's t-test. The degree of influence of the two-level qualitative indicator of the predictor on the two-level qualitative indicator of the response was assessed by calculating the odds ratio (OR). The homogeneity of the distribution of the qualitative indicator in two or more groups (or the quality of their relationship) was studied and evaluated by constructing conjugacy tables with subsequent calculation and evaluation of Pearson's $\chi 2$ criterion and Fisher's exact criterion [1]. Comparative evaluation of mean values in three or more groups was performed using single-factor analysis of variance [21].

Survival duration of patients of different groups and at different values of predictor signs was estimated using the mathematical and statistical method Survival Analysis and such procedures of the method as:

- calculation of descriptive characteristics of life time in the form of a life table (Life tables and Distribution) by a separate group of patients;
- calculation and construction of Kaplan-Meier curves for individual patient groups (Kaplan and Meier prodact-limit method);

- comparison of life expectancy of two groups of patients by constructing Kaplan-Meier curves and survival tables (Comparing twu samples);
- comparing the survival time of three or more groups of patients by constructing Kaplan-Meier curves and survival tables (Comparing multiple samples);
- construction of a mathematical model of survival (Proportional hazard (Cox) regression) to determine the prediction of the function (time) of survival of a certain group of patients and the degree of influence on it of the features (predictors) included in the model, in the form of odds ratio (OR) and its 95% confidence intervals [21].

2.6 Building mathematical models of survival and outcomes patients with metastatic renal cell cancer

To solve the problem of creating a multifactorial mathematical and statistical model for calculating the probability of patient survival within 5 years after surgical intervention, a matrix of training information was created. The matrix was based on a database containing laboratory and clinical data and the results of a 10-year follow-up of 981 patients. In accordance with the objectives of the study, the matrix included patients who lived for 5 years and more, as well as those who died within 5 years after surgical intervention. This group included 564 patients, of whom 475 (84.2%) died and 89 (15.8%) survived for a follow-up period of 5 years. The tool used was Statistica software- logistic regression model generation and SPSS for Windows software- model estimation using ROC curve. The method of logistic regression was chosen as a mathematical and statistical method of solving the problem, the main condition for using which is the dichotomous nature of the predicted sign, as well as qualitative predominantly dichotomous signs predictors.

Data processing was performed using IBM SPSS Statistics package (version 26) and R Studio (free software development environment for R programming language designed for statistical data processing) [7, 9].

Thus, all the provisions and conclusions made in the work are based on versatile and adequate to the research materials mathematical and statistical methods. Modern computational tools and their software were widely used.

Chapter 3
STUDY OF THE IMPACT OF CLINICAL AND MORPHOLOGIC FACTORS ON SURVIVAL OF PATIENTS WITH METASTATIC RENAL CELL CANCER

Currently, in the personalized treatment of mRCC in terms of rational use of drug therapy and the possibility of cytoreductive surgery, clinical oncologists have developed approaches to individualize antitumor treatment and identified some factors as tools for patient selection. Assessments of prognostic factors for patients with mRCC receiving systemic therapy have been used routinely but have limited accuracy [195]. mRCC is a heterogeneous disease and survival rates can be affected not only by individual factors (sex, age, tumor histological subtype, number and localization of metastases) but also by their combinations. Models used to determine prognosis include a variety of factors. In this chapter, the influence of additional clinical, morphologic, and laboratory factors on the survival of patients treated with systemic therapy is studied.

In the first stage, the 3- and 5-year survival rates and median OS in the study group (N=981) were determined (Figure 3.1).

In the presented Kaplan-Meier curves, the 3-year, 5-year OS rates in the overall cohort of patients were 49.4±1.5% and 28.2±1.4%, respectively. In addition, as shown in Figure 3.1. the mRCC patient cohort was heterogeneous. The median OS was 45.2 months, however, about 10% of mRCC patients die before 12 months and another part of about 30% live for more than 5 years.

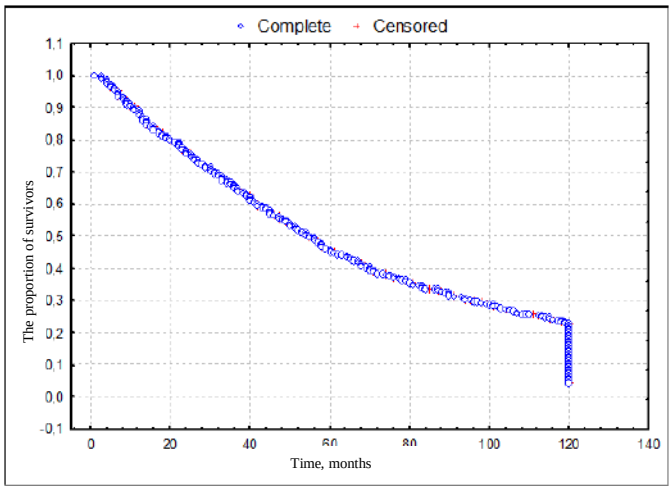


Figure 3.1 – OS rates in the total cohort of mRCC patients (N=981)

Similar data to our study were obtained in the work of S. Demasure et al. [179, 261]. In our study we also ask the question, what is the difference between the group of long-lived mRCC patients and patients with a life expectancy of less than a year? And what additional prognostic factors can influence the increase of survival rates?

Therefore, we have studied various factors that affect survival rates.

3.1 Survival rates for patients with metastatic renal-cell carcinoma as a function of clinical characteristics

The mean age of the patients was 60.8±9.7 years (22 years to 95 years), and the distribution of patients according to age is presented in Table 3.1 and Figure 3.2.

Table 3.1 – Distribution of mRCC patients according to age

Age	Number of patients	HR
18-44	45 (4.6)	–
45-59	395 (40.3)	0.81 (0.57-1.14, p=0.223)
60-74	464 (47.3)	0.89 (0.63-1.26, p=0.519)
above 75	77 (7.8)	1.10 (0.73-1.65, p=0.647)

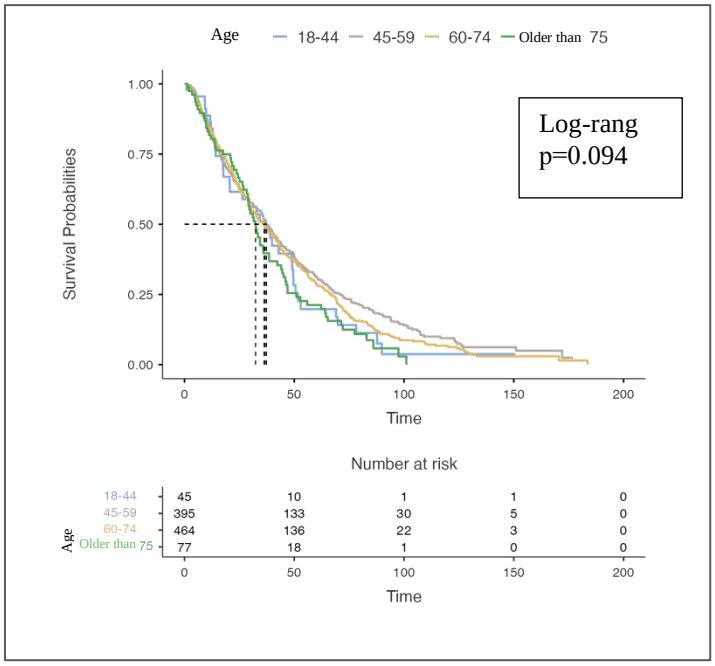


Figure 3.2 – Kaplan-Meier curves of OS indicators of patients with mRCC (N=981) as a function of age

The first factors that were studied in clinical characteristics were age, gender, primary tumor localization, and somatic status in mRCC patients.

The presented Kaplan-Meier curve plot shows that the 3-year and 5-year OS rates of young-aged patients (18-44 years) were 50.85% [37.43-69.09%, 95% CI] and 19.78% [10.27-38.08%, 95% CI] respectively and was not different at ages 45-59 years 52.24% [47.39-57.58%, 95% CI] and 31.48% [27.00-36.70%, 95% CI] respectively and at ages 60-74 years 50.28% [45.73-55.29%, 95% CI] and 28.72% [24.6-33.58%, 95% CI] respectively. However, the 3-year and 5-year OS in patients older than 75 years was 39.67% [29.2-52.76%, 95% CI] and 21.25% [13.58-33.24%, 95% CI], respectively. The median OS was 36.7 [20.6-49.6, 95% CI], 37.3 [34.1-42.4, 95% CI], 36.3 [31.7-41.2, 95% CI], and 32.4 [28.9-38.6, 95% CI] months, respectively. There were no statistically significant differences according to age (p=0.094). Thus, survival rates in young and middle-aged mRCC patients did not differ from the elderly and senile group. In the work of Xiuqiong Chen et al. mRCC patients older than 70 years had better OS compared with patients younger than

70 years (HR, 0.65; 95% CI, 0.48-0.89), but there was no significant difference in PFS between the two groups (HR, 0.73; 95% CI, 0.51-1.06) [160].

When assessing the gender composition of the study cohort, it was found that in our work, men predominated – 704 patients (71.8%), women were 277 (28.2%). HR 0.86 (0.74-1.00, p=0.055).

The results of calculating survival rates according to gender are presented in Figure 3.3.

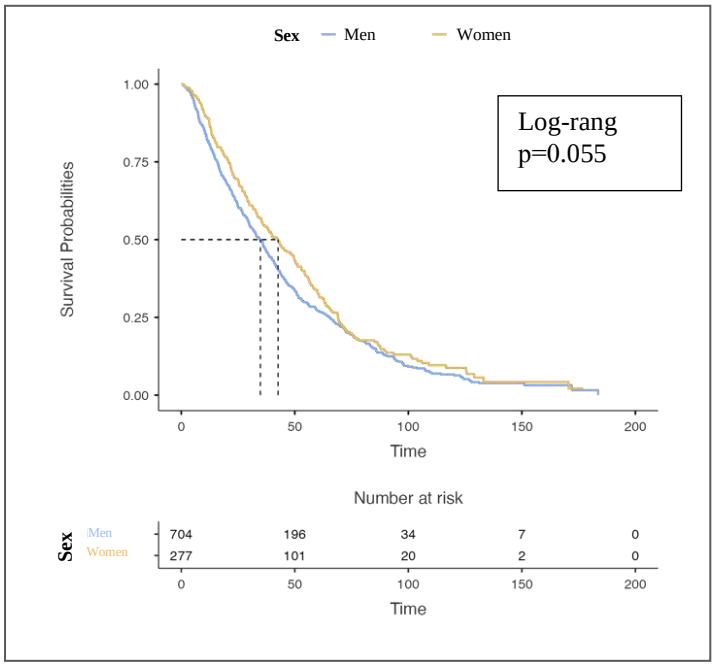


Figure. 3.3 – Kaplan-Meier curves of OS indicators of mRCC patients (N=981) according to gender

As shown in Figure 3.3, the 3-year and 5-year OS rates for women and men were 54.8% [49.0-61.3%, 95% CI] and 33.1% [27.7-39.6%, 95% CI], 48.5% [44.8-52.5%, 95% CI] and 27.2% [23.9-31.0%, 95% CI] (p=0.055), With a median OS of 34.9 [31.1-37.7, 95% CI] and 42.6 [35.4-50.1, 95% CI] months, respectively. However, the differences were not statistically significant (p=0.055). And in Xiuqiong Chen et al, men had worse OS than women (OR 1.48; 95% CI 1.14-1.93) [160].

When assessing the primary tumor localization of the patients included in the study, renal tumor localization was approximately the same: left renal tumor was

detected in 482 (49.1%) patients, right renal tumor in 475 (48.4%) patients, bilateral lesion was diagnosed in 24 (2.5%) patients (Table 3.2, Figure 3.4).

Table 3.2 – Distribution of mRCC patients depending on the location of the primary tumor

Localization of the primary tumor	Number of patients	HR
On the right	482 (49.1)	–
From left	475 (48.4)	0.96 (0.83-1.10, p=0.523)
Bilateral	24 (2.4)	0.99 (0.62-1.57, p=0.957)

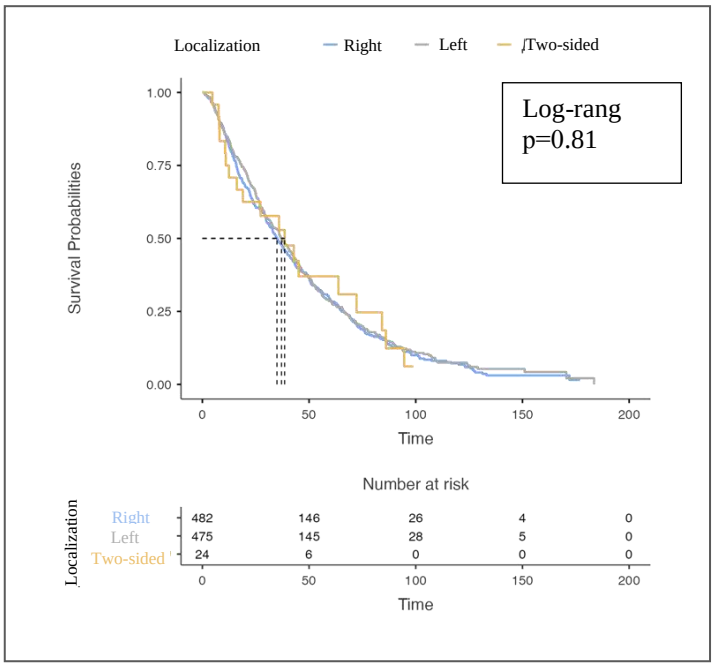


Figure 3.4 – Kaplan-Meier curves of OS indices of mRCC patients (N=981) depending on the side of the primary tumor lesion

Survival analysis showed that 3-year and 5-year OS rates depending on the location of the primary kidney tumor of patients were 51.63% [47.15-56,53%, 95% CI] and 28.57% [24.53-33.28%, 95% CI], on the right – 48.73% [44.29-53.62%, 95% CI] and 28.84% [24.82-33.51%, 95% CI], when both kidneys were affected – 52.88% [35.91-77.87%, 95% CI] and 37.02% [21.13-64.85%, 95% CI], respectively. The median OS was 37.1 [32.8-41.7, 95% CI], 35 [31.4-39.8, 95% CI], and 38.6 [19-84.2,

95% CI] months, respectively (p>0.05). Thus, the study revealed no statistically significant differences in OS and median OS depending on the location of the primary tumor (p=0.81).

In most of the patients in our study, somatic status was assessed using the ECOG scale, as shown in Table 3.3.

Table 3.3 – Distribution of mRCC patients depending on somatic status according to ECOG scale

ECOG	Number of patients	HR
0	57 (5,8)	–
1	399 (40,7)	1,45 (1,03-2,05, p=0,033)
2	347 (35,4)	2,75 (1,95-3,88, p<0,001)
3	178 (18,1)	9,38 (6,50-13,52, p<0,001)

Thus ECOG 0 was noted in 57 (5.8%) patients, ECOG1 in 399 (40.7%), ECOG2 in 347 (35.4%) and ECOG3 in 178 (18.1%) patients, respectively. Thus, most of the patients included in our study had ECOG 1 or 2 status and amounted to 76.1%. Table 3.3 also shows that one in five patients had very low somatic status and accounted for 18.1%.

As can be seen in Figure 3.5, OS rates are directly related to the general condition of the patients at the time of staging of metastatic RCC.

Thus, for ECOG0 status, the 3-year and 5-year OS rates of patients were 82.829% [72.648-94.437%, 95% CI] and 73.543% [61.701-87.658%, 95% CI], respectively. With ECOG1, 69.303% [64.663-74.277%, 95% CI] and 44.848% [39.788-50.551%, 95% CI], respectively. At ECOG2, 44.894% [39.815-50.622%, 95% CI] and 18.872% [15.017-23.716%, 95% CI], respectively. For ECOG3, it was 10.868% [7.111-16.609%, 95% CI] and 2.692% [1.052-6.888%, 95% CI], respectively.

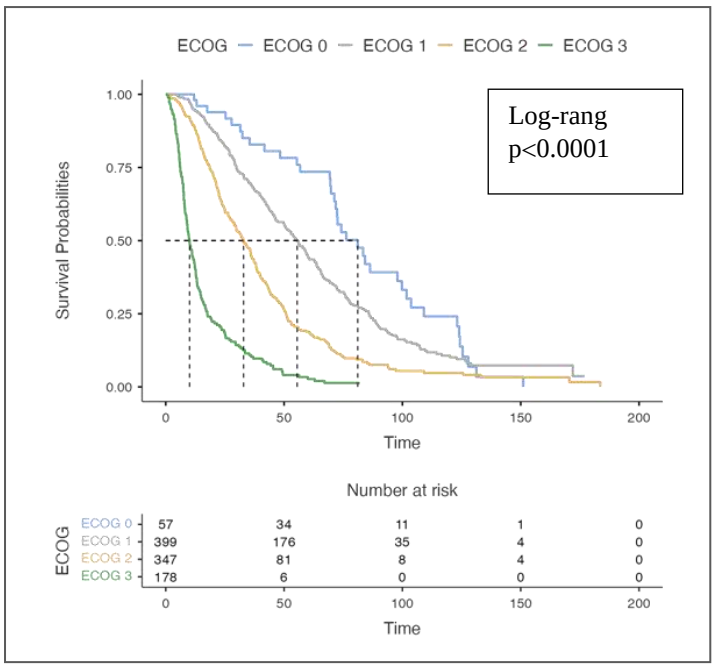


Figure 3.5 – Kaplan-Meier curves of OS indicators of mRCC patients (N=981) depending on ECOG status

The median OI for ECOG0 status was not reached. The median OS at ECOG 1, 2, 3 was 55.5 [50.5-60.2, 95% CI], 32.9 [29.5-36.3, 95% CI], and 10.1 [8.9-12.2, 95% CI] months, respectively. Group differences were statistically significant ($p<0.0001$). Thus, ECOG status is an important factor for predicting OS, as noted in the work of K. Takahara et al. [207].

The IMDC prognostic scale includes indicators such as Karnofsky somatic status <80%, serum corrected $Ca2+$ concentration >10 mg/dL, hemoglobin level <13 g/dL, time from diagnosis to initiation of drug therapy <1 year, neutrophil count >BGN*, and platelet count >BGN. It is possible that the significance of this model is related to indicators such as ECOG status and other laboratory and clinical indicators, which will be discussed separately.

Despite the fact that we consider separately all factors included in the prognostic model according to IMDC, we allowed ourselves to estimate survival rates in 3 prognostic groups in the total cohort of patients. When evaluating the patients included in the study according to the number of prognostic factors according to the IMDC classification, the patients were categorized into 3 groups. Table 3.4 shows

that the number of patients with favorable prognosis was 226 (23.0%), intermediate and unfavorable prognosis 352 (35.9%) and 403 (41.1%) patients, respectively. Thus, more than 75% of patients were from the intermediate and unfavorable prognosis groups.

Table 3.4 – Distribution of mRCC patients depending on the number of prognostic factors according to the IMDC scale

IMDC Forecast	Number of patients	HR
Favorable	226 (23.0)	–
Intermediate	352 (35.9)	1.97 (1.62-2.41, p<0.001)
Poor	403 (41.1)	4.28 (3.53-5.19, p<0.001)

As can be seen in Figure 3.6, OS performance is directly related to IMDC prognosis.

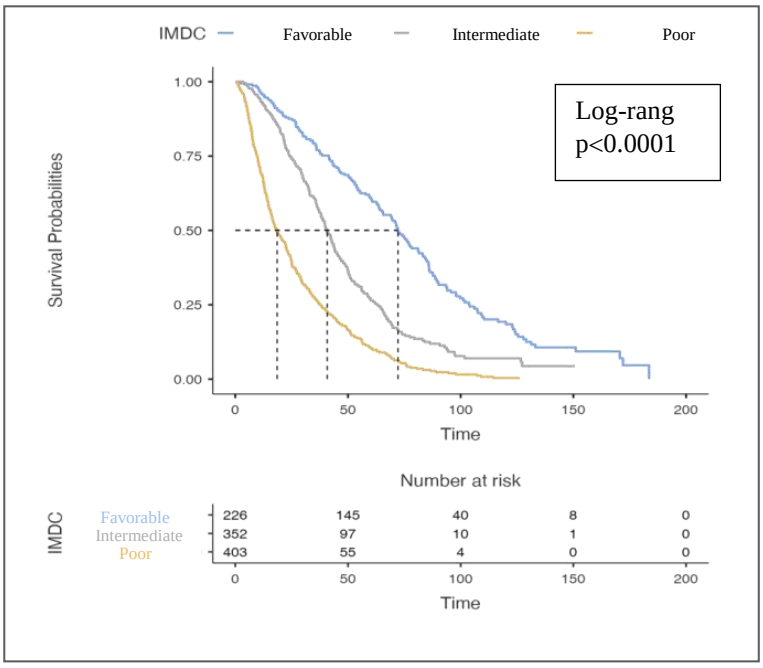


Figure 3.6 – Kaplan-Meier curves of OS indicators of mRCC patients (N=981) depending on IMDC prognosis group

Thus, in the favorable prognosis group the 3-year and 5-year OS of patients made 77.47% [72.16-83.2%, 95% CI] and 61.06% [54.90-67.9%, 95% CI], respectively, in the intermediate prognosis group – 58.76% [53.49-64.6%, 95% CI] and 26.83% [22.09-32.6%, 95% CI], respectively. And the OB rates in the unfavorable prognosis group were 26.65% [22.49-31.6%, 95% CI] and 10.46% [7.69-14.2%, 95% CI], respectively. The median OS was 72.2 [65.2-81.4, 95% CI], 40.8 [38.1-44, 95% CI], and 18.6 [16.2-22.5, 95% CI] months, respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on IMDC prognosis ($p<0.0001$). Patients with unfavorable prognosis have sharply decreased OS [57, 259].

Thus, based on our study, the somatic status of patients and IMDC prognostic groups should be considered in the clinical characteristics of prognosis in mRCC patients.

3.2 Study of the influence of tumor morphological characteristics on survival rates in patients with metastatic renal cell cancer

Morphological factors studied in our study were histological subtype and degree of tumor differentiation according to Fuhrman in mRCC patients.

When evaluating the mRCC patients included in the study depending on the histologic variant, the absolute majority of cases were verified as clear cell carcinoma – 867 (88.4%) patients. Non-small cell variants accounted for 114 (11.6%) cases, among them: papillary cancer – 46 (4.6%), chromophobe cancer – 19 (1.9%); other histologic variants (cancer from Bellini collecting tubes, medullary and tubulocystic cancer) were diagnosed in 49 (5.1%) patients (Table 3.5).

Table 3.5 – Distribution of mRCC patients depending on the histological subtype of the primary tumor

Histologic variant	Number of patients	HR
Clear cell cancer	867 (88.4)	–
Non-clear cell cancer	114 (11.6)	1.97 (1.59-2.43, p<0.001)

As can be seen in Figure 3.7, OS rates are directly related to the histologic variant of the tumor.

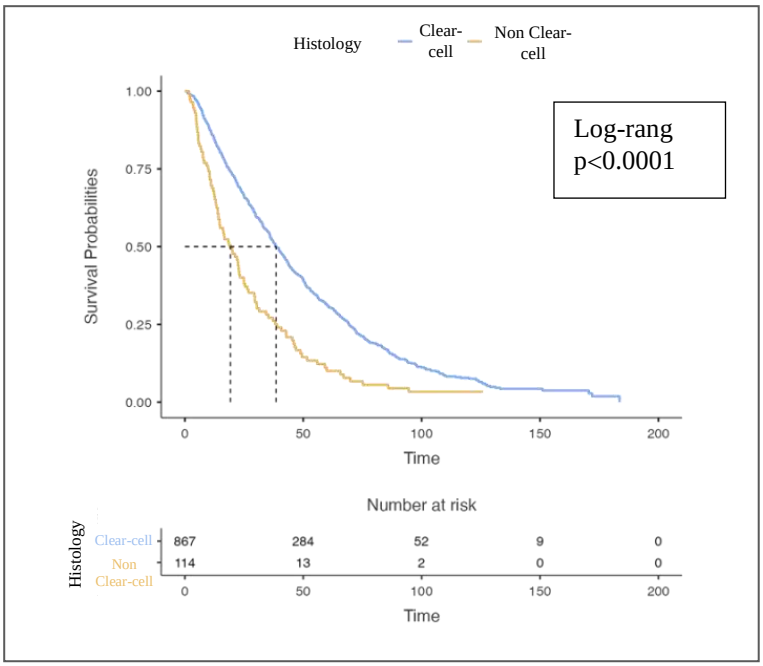


Figure 3.7 – Kaplan-Meier curves of OS indices of mRCC patients (N=981) depending on the histological variant of tumor

Thus, in the presented diagram of Kaplan-Meier curves, the 3-year and 5-year OS rates were 53.3% [49.9-56.9%, 95% CI] and 31.3% [28.2-34.8%, 95% CI], respectively, in the light-cell carcinoma variant, and 27.1% [19.8-37.1%, 95% CI] and 10.0% [5.5-18.3%, 95% CI], respectively, in the non-small-cell carcinoma variant. Meanwhile, the median OS was also higher in patients with non-small cell mRCC and was 38.5 [35.9-42.3, 95% CI] and 19.2 [14.7-24.9, 95% CI] months,

respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on the histological subtype of the tumor ($p<0.0001$), with the clear-cell variant being the most favorable. In current studies, the histologic subtype of the tumor is an important factor affecting survival rates in mRCC patients. In the work of S. Dudani et al. patients with luminal mRCC in contrast to patients with papillary mRCC, as a rule, had higher survival rates [100].

When evaluating the patients included in the study depending on the grade of differentiation according to the Fuhrman tumor scale were distributed as follows. Table 3.6 shows that the number of patients with Grade 1 was 186 (19.0%), with Grade 2 and Grade 3 360 (36.7%) and 435 (44.3%) patients, respectively. Thus, more than 80% of patients had moderately and low-differentiated tumors.

Table 3.6 – Distribution of patients depending on the degree of tumor differentiation according to Fuhrman

Grade	Number of patients	HR
1	186 (19.0)	–
2	360 (36.7)	1.88 (1.53-2.30, p<0.001)
3	435 (44.3)	3.30 (2.70-4.02, p<0.001)

As shown in Figure 3.8, the OS rates depended on tumor differentiation according to Fuhrman and the 3-year and 5-year OS rates were 76.1% [70.1-82.6%, 95% CI] and 62.4% [55.6-69.9%, 95% CI] at Grade 1, and 57.4% [52.3-63.0%, 95% CI] and 28.7% [24.0-34.3%, 95% CI] at Grade 2. And the OB rates at Grade 3 were only 32.5% [28.2-37.5%, 95% CI] and 12.9% [9.9-16.9%, 95% CI], respectively. The median OS also differed significantly depending on the grade of tumor differentiation and was 72.2 [65.5-80.5, 95% CI], 41.6 [37.3-45.2, 95% CI] and 22.1 [19.2-25, 95% CI] months, respectively. This indicator is by far the most important factor for predicting OS in mRCC patients and this has also been reflected in current studies [111].

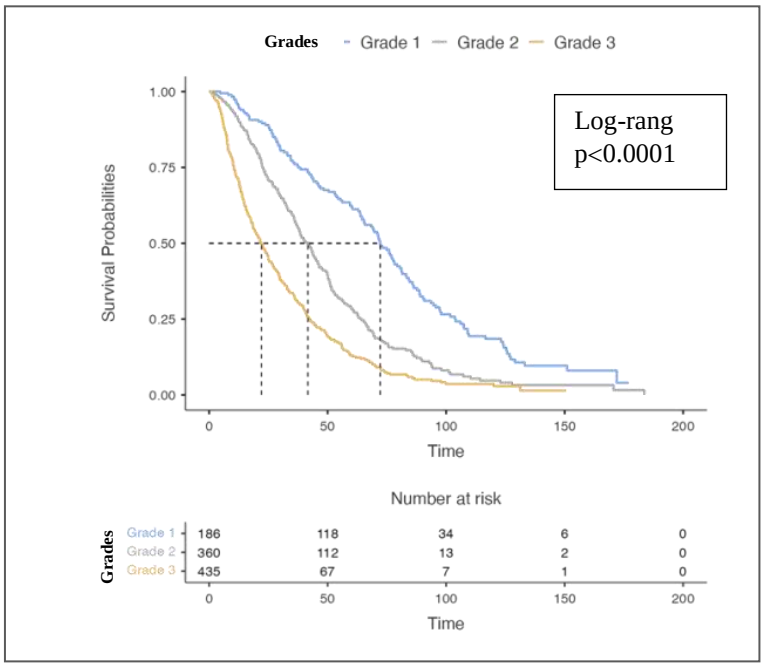


Figure 3.8 – Kaplan-Meier curves of OS indices of mRCC patients (N=981) depending on tumor differentiation according to Fuhrman

Thus, not only the histologic subtype but also the degree of tumor differentiation should be considered in morphologic characteristics of prognosis in mRCC patients.

3.3 Assessing the impact of laboratory data on survival rates of patients with metastatic renal cell cancer

Various laboratory findings may serve as prognostic factors and influence survival rates in mRCC patients. Detected hypercalcemia served as a predictor of mortality and was associated with a worse prognosis. The presence of anemia, elevated ESR and alkaline phosphatase contributed to worse prognosis and survival of patients with mRCC. According to the literature, worse survival rates have been described in patients with thrombocytosis, elevated neutrophils, C-reactive protein and LDH [61].

To identify additional prognostic factors for mRCC patients, we evaluated the impact of changes in laboratory parameters on survival rates of mRCC patients.

When evaluating various clinical and biochemical blood counts, it was found that the EF was worse in patients with anemia, making hemoglobin level an important prognostic factor. Increase of platelets in peripheral blood influenced the OB indices in patients with mRCC. No statistically significant differences were found for survival rates depending on the peripheral blood neutrophil count. Elevation of ESR influenced the survival rates of mRCC patients. The level of ionized calcium in peripheral blood influenced the indices of OS.

We next evaluated those laboratory parameters that had a statistically significant effect on survival rates in mRCC patients, which include hemoglobin, alkaline phosphatase, lactate dehydrogenase, and platelet and ESR levels.

When evaluating the patients included in the study depending on the hemoglobin level were distributed as follows. Thus, normal hemoglobin level was noted in 673 (68.6%) patients and anemia was noted in 308 (31.4%) patients. Thus, one third of the mRCC patients in our study had anemia, as shown in Table 3.7.

Table 3.7 – Distribution of patients depending on hemoglobin level

Hemoglobin	Number of patients	HR
Hemoglobin's normal	673 (68.6)	–
Anemia	308 (31.4)	2.62 (2.26-3.03, p<0.001)

As shown in Figure 3.9, the 3-year and 5-year OS rates for normal and anemic hemoglobin were 63.6% [59.9-67.56%, 95% CI] and 37.0% [33.3-41.14%, 95% CI], 21.2% [16.9-26.48%, 95% CI], and 11.3% [8.1-15.71%, 95% CI], respectively. The median OS also differed by hemoglobin level and was 46 [43-50.3, 95% CI] and 15 [14-17.3, 95% CI] months, respectively.

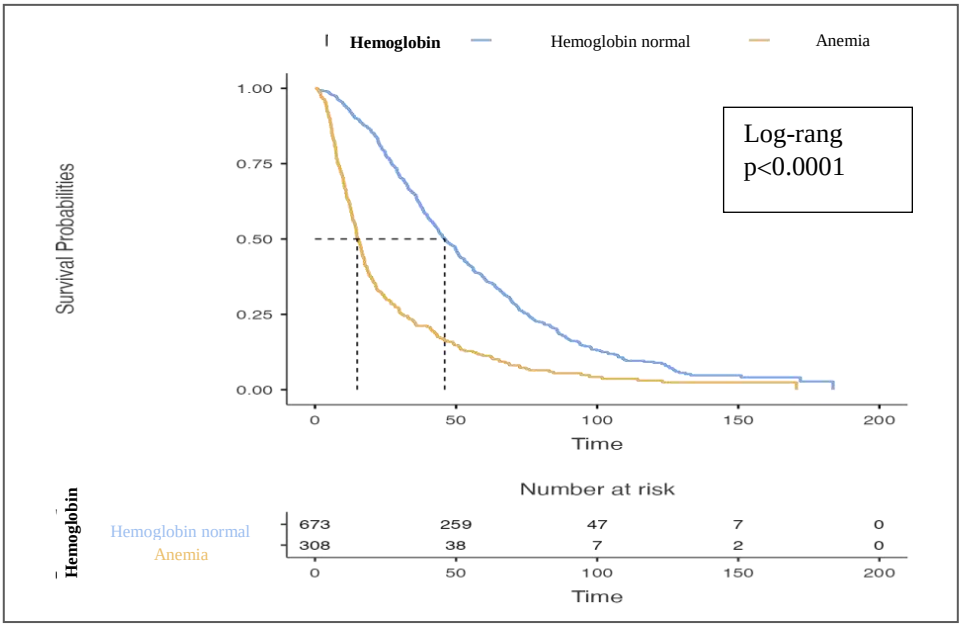


Figure 3.9 – Comparison of OS indicators of mRCC patients (N=981) depending on hemoglobin levels

Thus, the study revealed statistically significant differences in OS and median OS depending on hemoglobin level (p<0.0001). In modern studies, hemoglobin is an important factor affecting survival rates in patients with mRCC [61].

When evaluating the patients included in the study depending on the level of alkaline phosphatase (ALP) were distributed as follows. Thus, as can be seen from Table 3.8, a normal alkaline phosphatase level was found in 637 (64.9%) patients, and elevation of this index was noted in 344 (35.1%) patients. Thus, 2/3 of patients with mRCC had normal alkaline phosphorus levels.

Table 3.8 – Distribution of patients depending on the level of alkaline phosphorus

Alkaline phosphatase	Number of patients	HR
Norma	637 (64.9)	–
Above normal	344 (35.1)	1.57 (1.36-1.81, p<0.001)

Dependence of survival rates of mRCC patients on the level of alkaline phosphorus in peripheral blood (normal for women – 35-105 U/L, for men – 40-130 U/L), which is presented in Figure 3.10.

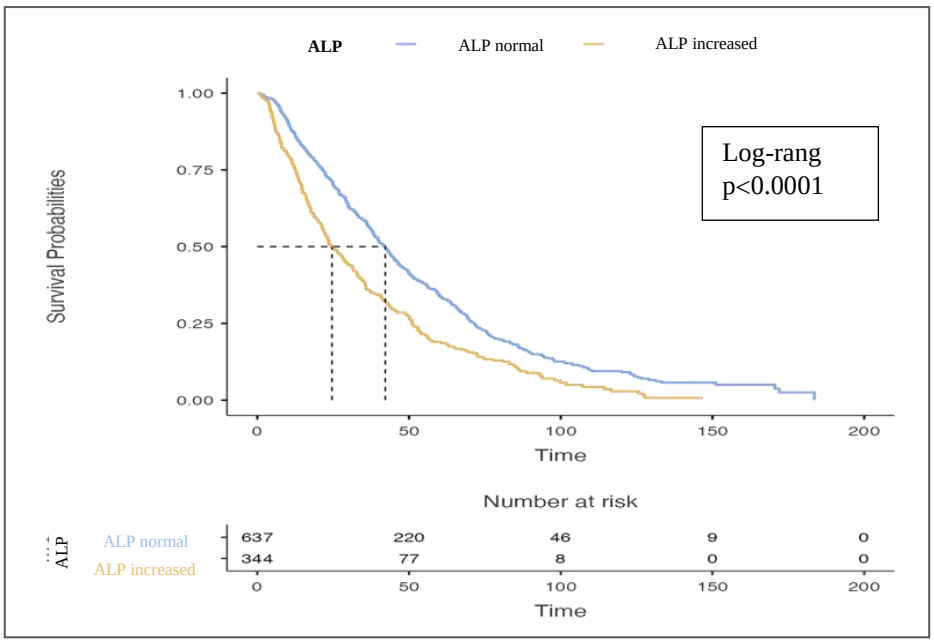


Figure 3.10 – Kaplan-Meier curves of OS indices of mRCC patients (N=981) depending on the level of alkaline phosphorus (ALP)

As shown in Figure 3.10, the OS rates depended on the level of alkaline phosphorus and the 3-year and 5-year OS rates for normal and elevated alkaline phosphorus were 57.7% [53.82-61.8%, 95% CI] and 34.2% [30.43-38.3%, 95% CI], 36.3% [31.31-42.0%, 95% CI] and 18.9% [14.97-24.0%, 95% CI], respectively. Meanwhile, the median OS also differed according to alkaline phosphate levels and was 42.2 [38.5-45.2, 95% CI] and 24.6 [21.9-29.9, 95% CI] months, respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on alkaline phosphorus levels ($p<0.0001$). In a study by Kyla Velaer et al. lactate dehydrogenase (LDH) and alkaline phosphate are factors that influence survival rates in mRCC patients [61].

When evaluating the patients included in the study depending on the level of LDH were distributed as follows. Thus, with normal LDH level was 722 (73.6%) patients, and elevation of this index was noted in 259 (26.4%) patients, which is shown in Table 3.9. Thus, more than 70% of mRCC patients had normal LDH levels.

Table 3.9 – Distribution of patients depending on LDH level

LDH	Number of patients	HR
Norma	722 (73.6)	–
LDH is above normal	259 (26.4)	1.36 (1.16-1.59, p<0.001)

Dependence of survival rates of mRCC patients on LDH level in peripheral blood (normal for women – 13-220 U/L, for men – 130-235 U/L), which is presented in Figure 3.11.

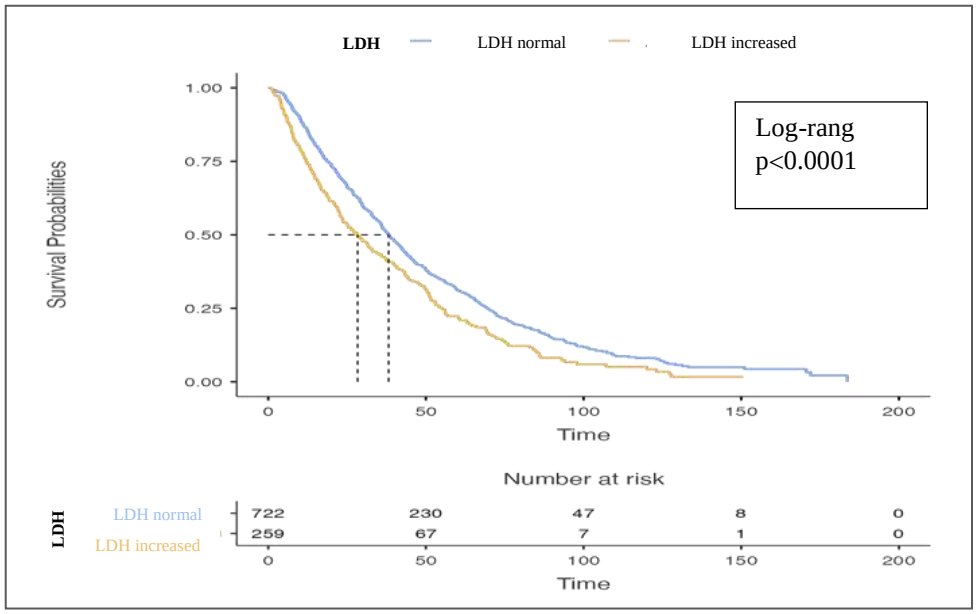


Figure 3.11 – Comparison of OS indicators of mRCC patients (N=981) depending on the level of LDH

As shown in Figure 3.11, the 3-year and 5-year OS rates for normal and elevated LDH were 53.0% [49.3-56.9%, 95% CI] and 31.2% [27.8-35.0%, 95% CI], 42.5% [36.7-49.3%, 95% CI] and 22.3% [17.5-28.5%, 95% CI], respectively. The median OS also differed according to LDH level and was 38.2 [35.8-41.8, 95% CI] and 28.3 [23.4-35.8, 95% CI] months, respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on LDH level (p<0.0001). In current studies, LDH is an important factor affecting survival rates in mRCC patients [128].

When evaluating the patients included in the study depending on the level of Erythrocyte sedimentation rate (ESR) were distributed as follows. Thus, at normal level of ESR amounted to 373 (38.0%) patients, and elevation of this index was noted in 608 (62.0%) patients, which is shown in Table 3.10. Thus, more than 60% of mRCC patients had elevated ESR values.

Table 3.10 – Distribution of patients depending on the ESR level

ESR	Number of patients	HR
ESR's normal	373 (38.0)	–
ESR's elevated	608 (62.0)	1.68 (1.45-1.94, p<0.001)

Dependence of survival rates of mRCC patients on the level of ESR in peripheral blood (normal for women – 2-20 mm/h, for men – 2-15 mm/h), which is presented in Figure 3.12.

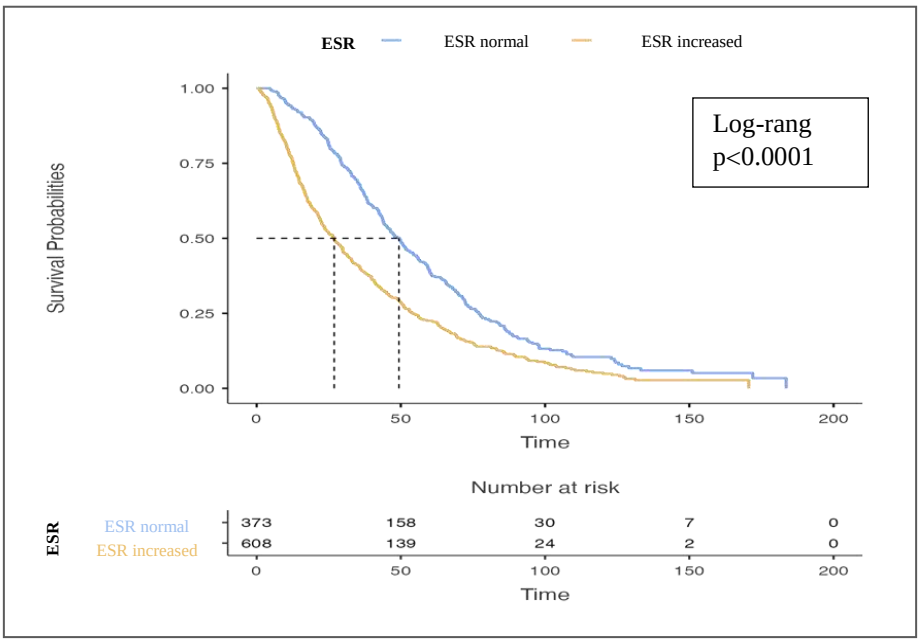


Figure 3.12 – Kaplan-Meier curves of OS indices of mRCC patients (N=981) depending on ESR level

As shown in Figure 3.12, the OB rates depended on the level of the ESR and the 3-year and 5-year OB rates for normal and elevated ESR were 67.09% [62.3-72.25%, 95% CI] and 38.99% [34.1-44.64%, 95% CI], 39.76% [35.9-44.05%, 95% CI] and 22.57% [19.2-26.47%, 95% CI], respectively. The median OS also differed according to ESR level and was 49.3 [44.1-55.4, 95% CI] and 26.9 [23.6-29.9, 95% CI] months, respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on the level of ESR ($p<0.0001$).

When evaluating the patients included in the study depending on the platelet level were distributed as follows. Thus, with normal platelet count was 679 (69.2%) patients, while thrombocytosis and thrombocytopenia were noted in 150 (15.3%) and 152 (15.5%) patients, as shown in Table 3.11. Thus, about 70% of mRCC patients had normal platelet counts.

Table 3.11 – Distribution of patients depending on platelet level

Platelets	Number of patients	HR
Platelets are normal	679 (69.2)	–
Thrombocytosis	150 (15.3)	1.71 (1.41-2.07, p<0.001)
Thrombocytopenia	152 (15.5)	1.35 (1.12-1.64, p=0.002)

As can be seen from Figure 3.13, the OS rates depend on platelet levels and the 3-year and 5-year OB rates with platelets normal and rising and falling were 56,5% [52.7-60.5%, 95% CI] and 32.4% [28.9-36.5%, 95% CI], 29.6% [22.8-38.3%, 95% CI] and 16.3% [11.0-24.0%, 95% CI], 42.4% [35.0-51.4%, 95% CI] and 25.2% [18.8-33.8%, 95% CI], respectively. The median OS also differed by platelet count and was 41.7 [38.1-44.3, 95% CI], 20.1 [15.5-25.3, 95% CI], and 28.9 [21.3-37, 95% CI] months, respectively.

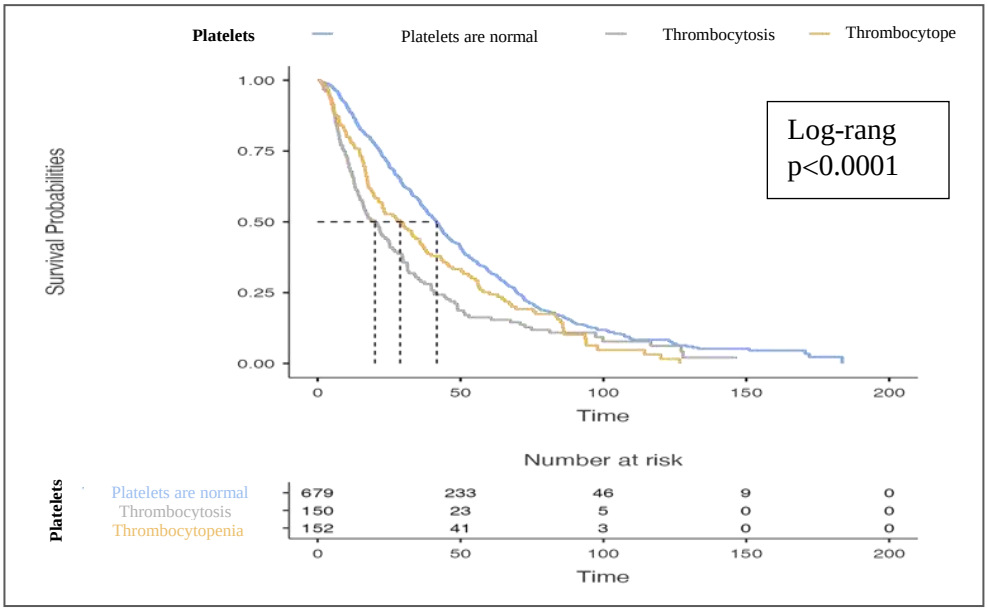


Figure 3.13 – Comparison of OS indicators of mRCC patients (N=981) depending on the platelet count

Thus, the study revealed statistically significant differences in OS and median OS depending on the platelet level (p<0.0001). In modern studies, platelets are an important factor affecting survival rates in patients with mRCC [209].

To complete the study to assess the impact of laboratory parameters on survival of mRCC patients, we performed single- and multivariate Cox analysis.

Table 3.12 shows that only hemoglobin level was a statistically significant factor influencing the OS indices in mRCC patients in single- and multivariate Cox analyses.

Table 3.12 – Cox single and multivariate analysis of only significant laboratory parameters in mRCC patients

Factors	Gradations	Number sick	Single-factor	Multifactorial
Hemoglobin	hemoglobin is normal	673 (68.6)	–	–
	anemia	308 (31.4)	2.62 (2.26-3.03, p<0.001)	2.28 (1.93-2.70, p<0.001)

Continuation of Table 3.12

Factors	Gradations	Number sick	Single-factor	Multifactorial
CF	alkaline phosphorus is normal	637 (64.9)	–	–
	alkaline phosphorus is elevated	344 (35.1)	1.57 (1.36-1.81, p<0.001)	1.10 (0.93-1.31, p=0.249)
LDH	LDH is normal	722 (73.6)	–	–
	LDH is elevated	259 (26.4)	1.36 (1.16-1.59, p<0.001)	1.05 (0.89-1.25, p=0.563)
ESR	ESR's normal	373 (38.0)	–	–
	ESR's elevated	608 (62.0)	1.68 (1.45-1.94, p<0.001)	1.16 (0.98-1.38, p=0.084)
Platelets	platelets are normal	679 (69.2)	–	–
	thrombocytosis	150 (15.3)	1.71 (1.41-2.07, p<0.001)	1.18 (0.95-1.46, p=0.139)
	thrombocytopenia	152 (15.5)	1.35 (1.12-1.64, p=0.002)	1.17 (0.96-1.44, p=0.129)

Thus, in single-factor analysis, hemoglobin, alkaline phosphatase, lactate dehydrogenase and platelet levels and ESR were statistically significant indicators, but in multivariate Cox analysis, only hemoglobin level was the most important factor affecting survival rates of mRCC patients.

3.4 Analysis of survival rates of patients in the group IMDC interim forecast

Additionally, the group of patients with intermediate prognosis mRCC was analyzed according to the number of risk factors present (Figure 3.14).

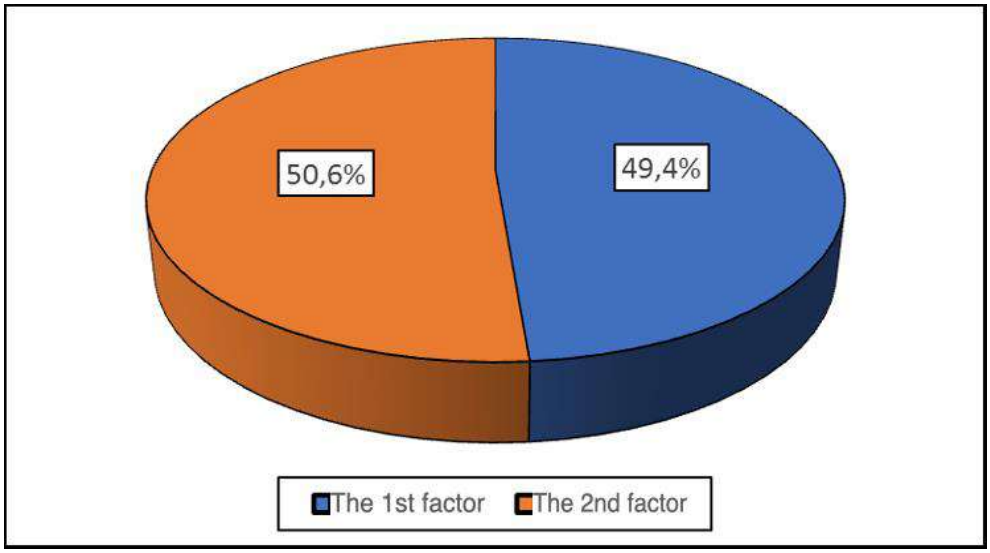
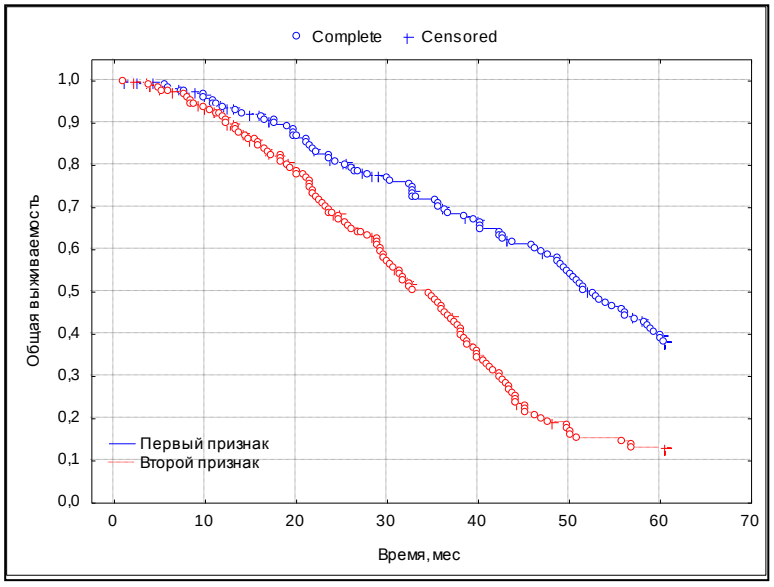


Figure 3.14 – Distribution of mRCC patients depending on the number of prognostic risk factors in the IMDC intermediate prognosis group

In our study, we compared survival rates according to the number of prognostic risk factors in the intermediate prognosis group of mRCC patients (Figure 3.15).



p<0,0001

Figure 3.15 – Kaplan-Meier curves of OS indicators of mRCC patients of intermediate prognosis (N=352) in the presence of one or two prognostic factors

The 3- and 5-year OS rates for the subgroups with risk factors 1 and 2 were 68.9±1.7% and 38.5±1.6%; 43.6±1.7% and 12.9±1.4%, respectively (p<0.0001). The median OS was 52 and 34 months, respectively.

Thus, in the present study, the intermediate prognosis group of mRCC patients is heterogeneous, and the number of prognostic risk factors according to IMDC had an impact on the OS rates.

In addition, we analyzed the factors that may influence the observed differences in survival rates in the group of patients with an intermediate prognosis (Table 3.13).

Table 3.13 – Comparison of the frequency of occurrence of parameters likely to influence prognosis in mRCC patients of intermediate prognosis according to IMDC

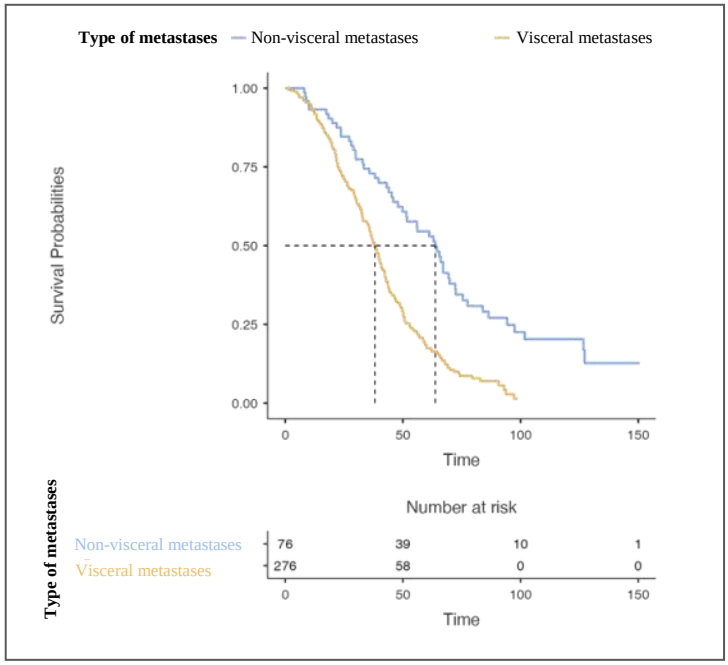
Characterization of patients	General n (%) (N=352)	1 factor n (%) (N=174)	2 factors n (%) (N=178)	$\chi2$= p-value
Men	250 (71)	126 (72.4)	124 (69.7)	$\chi2$=0.48
Women	102 (29)	48 (27.6)	54 (30.3)	p=0.49
Age, years	61.3 (median 32-84)	60.6 (median 33-83)	62.0 (median 32-84)	p=0.68
Performing a nephrectomy/kidney resection				
Yes	336 (95.5)	168 (96.5)	168 (94.4)	$\chi2$=1.2
No	16 (3.8)	6 (3.5)	10 (5.6)	p=0.28
T1-T2	131 (37.2)	64 (36.8)	67 (37.6)	$\chi2$=0.33
T3-T4	221 (62.8)	110 (63.2)	111 (62.4)	p=0.56
No	282 (80.1)	141 (81)	141 (79.2)	$\chi2$=0.005
N1	70 (19.9)	33 (19)	37 (20.8)	p=0.94
Tumor differentiation according to Fuhrman				
G1	34 (9.6)	23 (13.2)	11 (6.2)	$\chi2$=6.0
G2	195 (55.5)	93 (53.5)	102 (57.3)	p=0.045
G3	123 (34.9)	58 (33.3)	65 (36.5)	

Continuation of Table 3.13

Characterization of patients	General n (%) (N=352)	1 factor n (%) (N=174)	2 factors n (%) (N=178)	χ2= p-value
Histopathologic type Small cell Non-small cell	 321 (91.2) 31 (8.8)	 162 (93.1) 12 (6.9)	 159 (89.3) 19 (10.7)	 χ2=1.9 p=0.16
Number of affected organs at the time of treatment 1 2 3 or more	 143 (44.8) 100 (31.3) 73 (22.9)	 74 (48.0) 42 (27.3) 38 (24.7)	 69 (38.8) 58 (32.6) 35 (19.6)	 χ2=2.7 p=0.26
LDH levels	norma LDH>ULN	134 (77) 40 (23)	141 (79.2) 37 (20.8)	χ2=0.42 p=0.52
Alkaline phosphate levels	norma CF>ULN	117 (67.2) 57 (32.8)	122 (68.5) 56 (31.5)	χ2=0.30 p=0.58
Level of ionized calcium in peripheral blood	norma Ca>ULN Unknown	59 (33.9) 26 (14.9) 89 (51.2)	67 (37.6) 20 (11.2) 91 (51.2)	χ2=0.22 p=0.37
ESR	norma >ULN	69 (39.7) 105 (60.3)	79 (44.4) 99 (55.6)	χ2=0.03 p=0.86
Duration of treatment (months) (M±m)		67.6±3.8	54.1±2.7	p<0.01
Systemic therapy (months) (M±m)	1 line	14.6±1.05	11.8±1.03	p>0.05
	2 line	13.3±1.17	11.7±1.25	p>0.05
	line 3	15.1±1.59	10.3±1.78	p>0.05

Table 3.13 shows that patients with 1 prognostic risk factor had a higher incidence of G1 tumors (13.2/6.2) and a more favorable ECOG status. None of the laboratory parameters showed statistical differences in the frequency of its deviations from normal. Due to the previously demonstrated better OS of mRCC patients with 1 unfavorable prognostic risk factor according to IMDC, the duration of systemic therapy was statistically different, but no differences in the duration of its lines were revealed.

As can be seen in Figure 3.16, the rates of OS depended on the presence of nonvisceral or visceral metastases and the 3-year and 5-year OS rates for nonvisceral and visceral metastases were 92.4% [89.4-95.7%, 95% CI] and 54.6% [48.6-61.4%, 95% CI], 72.9% [63.2-84.2%, 95% CI] and 54.5% [43.8-67.9%, 95% CI], respectively (p<0.0001). The median OS was also higher in patients with non-visceral metastases and was 63.7 [51.5-72.5, 95% CI] and 38.1 [35.5-40.9, 95% CI] months, respectively.



p<0,0001

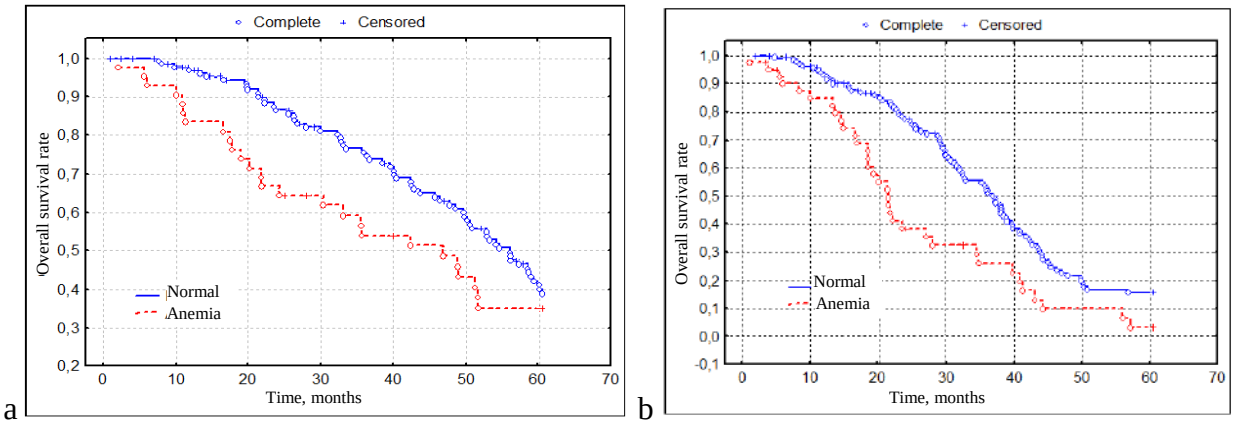
Figure 3.16 – Kaplan-Meier curves of OS indices of mRCC patients of intermediate prognosis (N=352) in the presence of nonvisceral and visceral metastases

Thus, the study revealed a statistically significant increase in OS and median OS in patients of intermediate prognosis according to IMDC in the presence of non-visceral metastases (p<0.0001).

3.4.1 Impact of laboratory data on survival rates of patients with metastatic renal cell cancer IMDC intermediate forecast groups

The above comparison of the characteristics of patients with mRCC of intermediate prognosis with 1 and 2 unfavorable risk factors demonstrated the absence of statistically significant differences for all laboratory parameters, therefore it is reasonable to evaluate their possible impact on survival rates.

We evaluated the impact of hemoglobin, platelet, ESR, and LDH levels on survival rates of mRCC patients in the presence of one or two IMDC risk factors (Figure 3.17).



p=0,016 p=0,00016

Figure 3.17 – Kaplan-Meier curves of OS indicators in mRCC patients with the presence of one (a) and two (b) prognostic risk factors with normal hemoglobin and anemia.

As can be seen from Figure 3.17, OS rates depend on hemoglobin level and the 3-year and 5-year OS rates at hemoglobin normal (135-160 and 120-140 g/L) in patients with factors 1 and 2 were 74.3±1.7% and 31.3±1.4%, 50.2±1.5% and 35.0±1.4%, respectively. Median OS at hemoglobin normal was 55 and 36 months, respectively (p=0.00016). The 3-year and 5-year OS rates for anemia (below 120-135 g/L) were 53.8±1.6% and 35.0±1.8% in patients with 1 factor and 27.8±1.5% and

1.9±1.3% when 2 factors were present. The median OS was also significantly different and was 47 and 22 months, respectively. Thus, the study revealed statistically significant differences in OS and median OS in patients with normal hemoglobin levels in patients with 1 unfavorable risk factor (p=0.016 and p=0.00016).

Figure 3.18 shows that the 3-year and 5-year OS rates for platelet normal (150-400 U/μL) patients were 70.2±1.7% and 32.2±1.5%, 42.8±1.5% and 12.5±1.3%, respectively. The median OS also differed and was 51 and 34 months. The 3-year and 5-year OS rates for thrombocytotic (above 400 U/μL) patients were 65.9±1.7% and 38.6±1.5%, 41.7±1.5% and 12.3±1.3%, respectively. Median OS was 55 and 22 months, respectively.

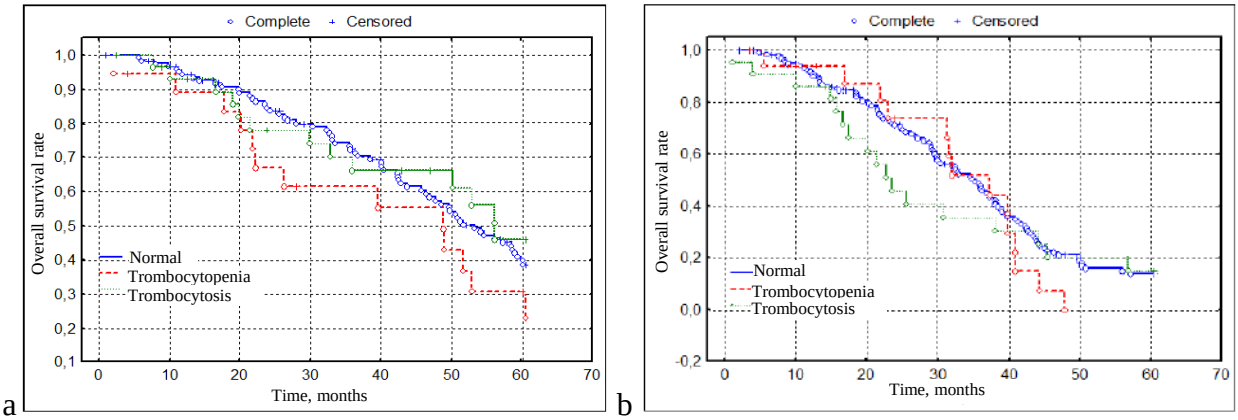
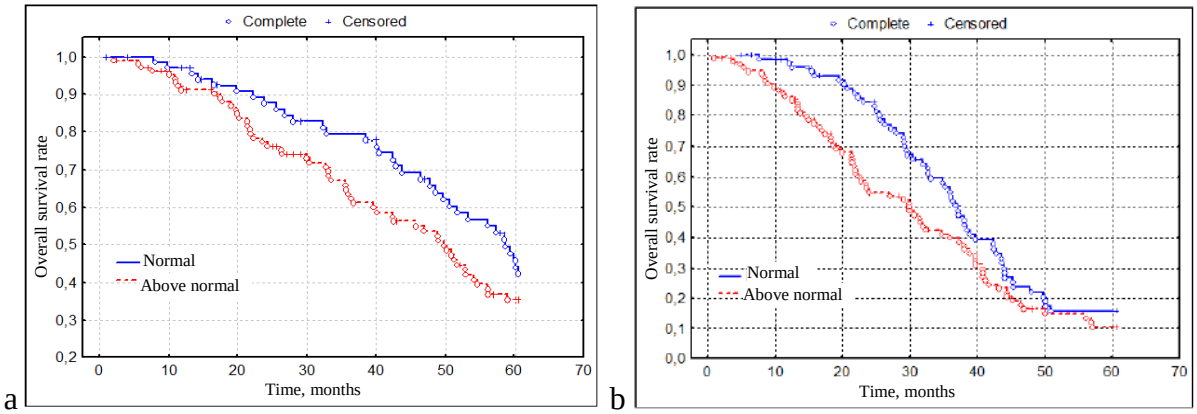


Figure 3.18 – Kaplan-Meier curves of OS indicators in mRCC patients with the presence of one (a) or two (b) prognostic factors depending on the platelet count in peripheral blood

Thus, platelet count did not affect the OS and median OS scores of patients in the intermediate prognosis group of mRCC patients depending on the number of unfavorable IMDC risk factors (p=0.34 and p=0.35).

The Kaplan-Meier curves presented in Figure 3.19 show that the 3-year and 5-year OS rates for normal (2-15 mm/h) ESR patients were 79.2±1.6% and 44.1±1.5% in patients with 1 adverse factor and 47.4±1.5% and 15.7±1.4%, respectively, when

2 factors were present. The median OS was also significantly different and was 58 and 37 months. The 3-year and 5-year OS rates for patients with elevated ESR (above 12-15 mm/h) were 61.4±1.6% and 34.8±1.5%, 40.1±1.5% and 10.4±1.3%, respectively. The median OS was 50 and 30 months.

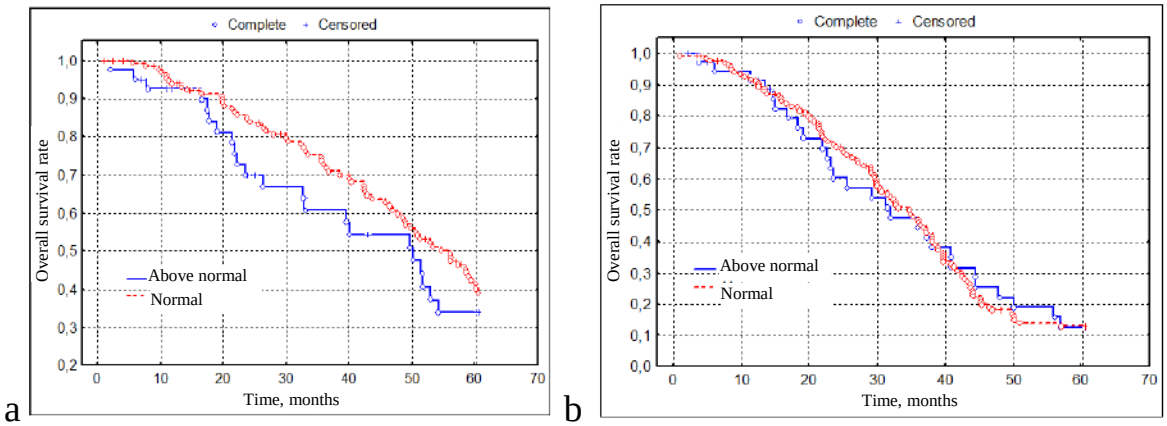


p=0,059 p=0,0028

Figure 3.19 – Kaplan-Meier curves of OS indicators in mRCC patients with the presence of one (a) or two (b) predictive factors ESR

Thus, the value of ESR had an impact on OS and median OS in mRCC patients of intermediate prognosis depending on the number of IMDC risk factors (p=0.059 and p=0.0028).

The presented Figure 3.20 Kaplan-Meier curves show that the 3-year and 5-year OS rates for LDH in normal (13-220 and 130-235 U/L) patients were 71.7±1.6% and 39.9±1.7% in patients with 1 unfavorable factor 42.2±1.5% and 13.0±1.3% when 2 factors were present. Median OS also differed and was 54 and 34 months. The 3-year and 5-year OS rates for patients with elevated LDH (above 220-235 U/L) were 60.7±1.6% and 33.6±1.3% for the 1-factor group 41.8±1.5% and 12.6±1.3%, respectively, for the presence of 2 factors. The median OS was 50 and 31 months. Thus, LDH level had no effect on the OS in patients with intermediate prognosis mRCC depending on the number of IMDC risk factors (p=0.15 and p=0.78).



p=0,155 p=0,78

Figure 3.20 – Comparison of Kaplan-Meier curves of OS and PFS indicators in mRCC patients with one (a) or two (b) prognostic factors for normal and elevated LDH

3.5 Single and multivariate analyses of proportional models Cox risks in patients with metastatic renal cell cancer of favorable, intermediate, and unfavorable renal cell cancer IMDC projections

After studying the influence of clinical and morphological factors on survival rates of mRCC patients in the overall cohort, we evaluated the influence of additional factors in the presence of favorable, intermediate and unfavorable prognosis according to the IMDC scale.

Based on the performed calculations, an attempt was made to search for the influence of additional prognostic factors on survival rates in mRCC patients based on the Cox proportional hazards model (Table 3.14).

Thus, Table 3.14 shows that, based on single and multivariate analysis, the degree of tumor differentiation, type and number of metastases, performance of NE, and presence of visceral metastases influenced the OS rates for 1 adverse risk factor in mRCC patients of intermediate prognosis according to IMDC.

Table 3.14 – Cox proportional hazards model of the effect on AE scores in the intermediate prognosis subgroup of mRCC patients with 1 IMDC prognostic risk factor (N=174)

Signs		Subtype intermediate 1			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Gender	male female	1.0 (0.6÷1.7)	0.88	0.9 (0.5÷1.6)	0.64
Localization of metastases	1, 2, 3	1.2 (0.8÷1.9)	0.33	1.3 (0.8÷2.2)	0.28
Degree of tumor differentiation	G 1, 2, 3	1.7 (1.2÷2.5)	0.006	1.7 (1.1÷2.6)	0.01
Type of metastasis	synchronous metachronous	0.4 (0.2÷0.6)	<0.001	0.4 (0.2÷0.7)	0.00
Number metastases	solitary single multiple	1.6 (1.1÷2.4)	0.02	2.0 (1.0÷3.8)	0.05
Number of organs metastatic	one, two three or more	1.2 (0.9÷1.6)	0.19	0.7 (0.4÷1.2)	0.20
CN	CN (±)	1.3 (0.9÷1.7)	0.002	1.8 (1.1÷2.5)	0.042
Visceral and nonvisceral metastases		1.2 (0.9÷1.6)	<0.001	1.7 (0.9÷2.2)	<0.001
Bones	0, 1	1.1 (0.7÷1.9)	0.64	0.8 (0.4÷1.6)	0.46
Lungs	0, 1	0.9 (0.5÷1.5)	0.71	0.8 (0.4÷1.7)	0.54
Liver	0, 1	1.6 (0.8÷3.2)	0.20	2.2 (0.8÷5.6)	0.12
Brain	0, 1	1.0 (0.5÷2.4)	0.90	1.3 (0.5÷3.7)	0.60
Lymph nodes	0, 1	1.6 (0.9÷2.6)	0.08	1.2 (0.5÷2.7)	0.68
Alkaline phosphatase	norm CF>ULN	1.2 (0.7÷1.9)	0.51	0.9 (0.5÷1.7)	0.75
LDH	norm >ULN	1.5 (0.8÷2.5)	0.18	1.1 (0.6÷1.5)	0.80
ESR	norm >ULN	1.3 (0.8÷2.1)	0.36	1.1 (0.6÷1.9)	0.87

Table 3.15 shows that in the single- and multivariate Cox proportional hazards model analysis, also tumor differentiation, type and number of metastases, performance of CN, and presence of visceral metastases influenced the OS rates in mRCC patients with 2 prognostic factors in the intermediate-risk population.

Table 3.15 – Cox proportional hazards model of the effect on OS scores in a subgroup of intermediate prognosis mRCC patients with 2 IMDC prognostic risk factors (N=178)

Signs		Subtype intermediate 2			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Gender	male female	0.7 (0.5÷1.1)	0.13	0.7 (0.5÷1.2)	0.18
Localization of metastases	1, 2, 3	1.0 (0.7÷1.3)	0.91	0.9 (0.6÷1.2)	0.45
Degree of tumor differentiation	G 1, 2, 3	2.2 (1.6÷3.0)	<0.001	1.7 (1.2÷2.4)	0.01
Type of metastasis	synchronous metachronous	0.4 (0.3÷0.5)	<0.001	0.3 (0.2÷0.5)	<0.001
Number metastases	solitary single multiple	2.1 (1.5÷3.0)	<0.001	2.5 (1.5÷4.0)	<0.001
Number of organs metastatic	one, two three or more	1.1 (0.9÷1.4)	0.25	1.0 (0.7÷1.4)	0.89
CN	CN (±)	1.4 (0.9÷1.9)	<0.001	1.2 (1.0÷2.1)	<0.001
Visceral and non-visceral. metastases		1.2 (0.9÷1.7)	<0.001	1.4 (1.1÷2.2)	<0.001
Bones	0, 1	1.1 (0.7÷1.6)	0.69	0.7 (0.4÷1.3)	0.32
Lungs	0, 1	1.3 (0.9÷1.9)	0.15	0.8 (0.5÷1.3)	0.34
Liver	0, 1	0.8 (0.5÷1.3)	0.35	0.7 (0.3÷1.6)	0.41
Brain	0, 1	0.8 (0.3÷2.6)	0.71	0.6 (0.2÷2.0)	0.40

Continuation of Table 3.15

Signs		Subtype intermediate 2			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Lymph nodes	0, 1	1.3 (0.9÷1.9)	0.11	1.0 (0.6÷1.5)	0.85
Alkaline phosphatase	norm CF>ULN	1.4 (1.0÷2.0)	0.6	1.2 (0.8÷1.9)	0.40
LDH	norm >ULN	0.9 (0.6÷1.4)	0.71	1.0 (0.6÷1.6)	0.92
ESR	norm >ULN	1.2 (0.8÷1.6)	0.41	0.8 (0.5÷1.4)	0.52

Table 3.16 shows that in the single-factor analysis of the Cox proportional hazards model, the degree of tumor differentiation and the number of metastases influenced PFS rates in the presence of 1 unfavorable risk factor in patients with mRCC of intermediate prognosis according to IMDC, while in the multifactor analysis, in addition to the previous factors, the type of metastases also had an impact.

Table 3.16 – Cox proportional hazards model of the effect on PFS scores in a subgroup of mRCC patients of intermediate prognosis by IMDC with 1 prognostic risk factor (N=174)

Signs		Subtype intermediate 1			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Gender	male female	1.0 (0.6÷1.6)	0.93	0.9 (0.5÷1.6)	0.64
Localization of metastases	1, 2, 3	1.2 (0.8÷1.7)	0.40	1.3 (0.8÷2.2)	0.28

Continuation of Table 3.16

Signs		Subtype intermediate 1			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Degree of differentiation	G 1, 2, 3	1.4 (1.1÷2.0)	0.02	1.7 (1.1÷2.6)	0.01
Type of metastasis	synchronous metachronous	1.0 (0.6÷1.6)	0.99	0.4 (0.2÷0.7)	0.00
Number metastases	solitary single multiple	1.4 (1.0÷2.0)	0.04	2.0 (1.0÷3.8)	0.05
Number of organs metastatic	one, two three or more	1.0 (0.8÷1.3)	0.83	0.7 (0.4÷1.2)	0.20
Bones	0, 1	0.9 (0.6÷1.4)	0.70	0.8 (0.4÷1.6)	0.46
Lungs	0, 1	1.1 (0.7÷1.7)	0.64	0.8 (0.4÷1.7)	0.54
Liver	0, 1	1.0 (0.5÷2.1)	0.93	2.2 (0.8÷5.6)	0.12
Brain	0, 1	1.4 (0.7÷2.9)	0.37	1.3 (0.5÷3.7)	0.60
Lymph nodes	0, 1	1.4 (0.9÷2.2)	0.17	1.2 (0.5÷2.7)	0.68
Alkaline phosphatase	norm CF>ULN	1.1 (0.7÷1.6)	0.74	0.9 (0.5÷1.7)	0.75
LDH	norm >ULN	1.3 (0.8÷2.1)	0.26	1.1 (0.6÷2.1)	0.80
ESR	norm >ULN	1.4 (0.9÷2.1)	0.14	1.1 (0.6÷1.9)	0.87

Table 3.17 shows that in the single-factor analysis of the Cox proportional hazards model, the type of metastases, their number, and the number of affected organs in the presence of 2 unfavorable risk factors in mRCC patients with intermediate prognosis according to IMDC had an impact on PFS. In multivariate analysis, the type and number of metastases had an impact.

Table 3.17 – Cox proportional hazards model of the effect on PFS scores in a subgroup of intermediate prognosis patients of mRCC patients with 2 prognostic risk factors according to IMDC (N=178)

Signs		Subtype intermediate 2			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Gender	male female	0.9 (0.6÷1.3)	0.60	0.8 (0.5÷1.2)	0.24
Localization of metastases	1, 2, 3	0.8 (0.6÷1.1)	0.27	1.0 (0.7÷1.4)	0.86
Degree of differentiation tumors	G 1, 2, 3	1.2 (0.9÷1.6)	0.18	1.1 (0.8÷1.6)	0.64
Type of metastasis	synchronous metachronous	1.4 (1.0÷2.1)	0.07	1.6 (1.0÷2.5)	0.03
Number metastases	solitary single multiple	1.6 (1.2÷2.1)	0.003	2.0 (1.3÷3.1)	0.00
Number of organs metastatic	one, two three or more	1.2 (1.1÷1.7)	0.01	1.1 (0.7÷1.7)	0.64
Bones	0, 1	1.3 (0.9÷1.9)	0.14	1.1 (0.6÷1.9)	0.86
Lungs	0, 1	1.2 (0.8÷1.7)	0.38	0.6 (0.4÷1.1)	0.10
Liver	0, 1	1.0 (0.6÷1.7)	0.93	0.7 (0.3÷1.6)	0.43
Brain	0, 1	1.7 (0.4÷6.8)	0.48	1.0 (0.2÷4.5)	0.98
Lymphatic nodes	0, 1	1.2 (0.8÷1.7)	0.30	0.8 (0.5÷1.4)	0.53
Alkaline phosphatase	norm CF>ULN	1.2 (0.8÷1.8)	0.28	0.8 (0.5÷1.3)	0.47
LDH	norm >ULN	1.0 (0.7÷1.5)	0.99	0.9 (0.6÷1.6)	0.79
ESR	norm >ULN	1.4 (1.0÷2.0)	0.05	1.3 (0.7÷2.3)	0.43

Thus, our study revealed a clear heterogeneity of the group of intermediate prognosis by IMDC in mRCC patients depending on the number (1 or 2) of unfavorable risk factors. The same data were obtained in the work of A. Sella et al. [116]. Based on single- and multivariate analysis in patients with mRCC of intermediate prognosis according to IMDC in the presence of 1 or 2 unfavorable risk factors, the degree of tumor differentiation according to Fuhrman, the type and number of metastases, as well as the performance of CN and the presence of visceral metastases influenced the OS indices.

We also calculated OS rates in patients with favorable and poor prognosis for nonvisceral and visceral metastases (Figure 3.21).

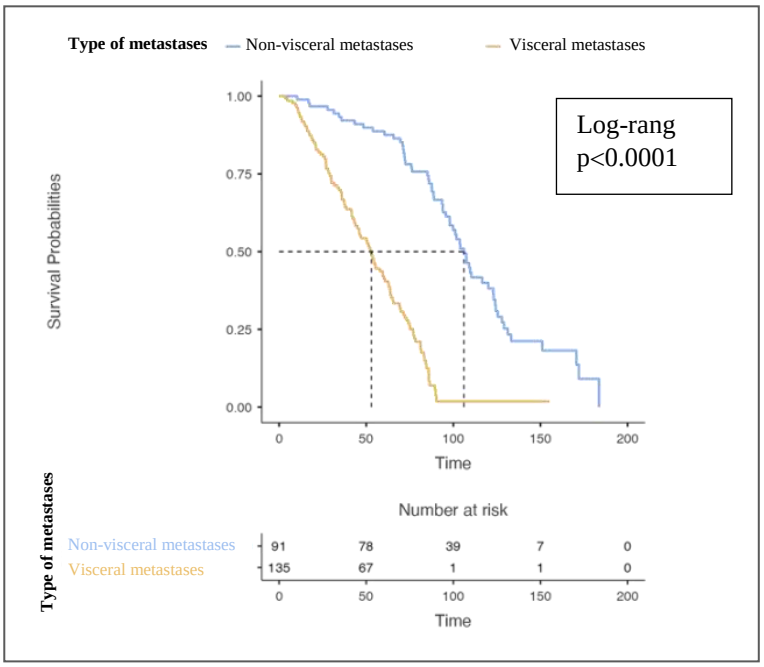


Figure 3.21 – Comparison of Kaplan-Meier curves of OS indicators in patients with favorable prognosis of mRCC (N=226)
in the presence of nonvisceral and visceral metastases

As shown in Figure 3.21, OS rates were directly related to the presence of nonvisceral or visceral metastases and the 3-year and 5-year OS rates for nonvisceral and visceral metastases were 92.2% [86.8-97.91%, 95% CI] and 88.7% [82.4-95.56%, 95% CI], 93.3% [89.2-97.63%, 95% CI] and 67.5% [60.0-75.98%, 95% CI],

respectively. The median OS was also higher in patients with nonvisceral metastases and was 106.1 [98-122.9, 95% CI] and 53 [45-60.8, 95% CI] months, respectively. Thus, the study revealed a statistically significant increase in OS and median OS in patients with favorable prognosis according to IMDC with non-visceral metastases (p<0.0001) (Figure 3.22).

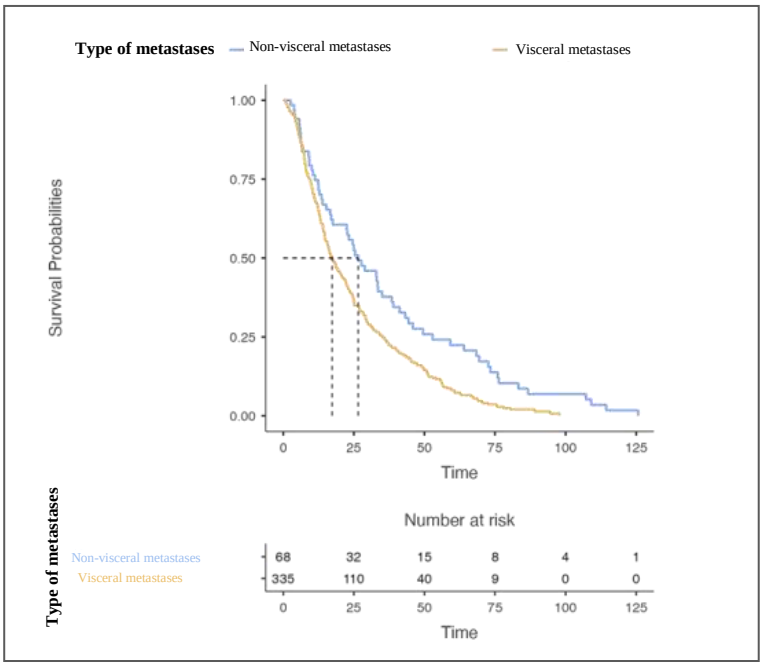


Figure 3.22 – Comparison of Kaplan-Meier curves of OS indicators of mRCC patients with poor prognosis (N=403) in the presence of nonvisceral and visceral metastases

As shown in Figure 3.22, OS rates depended on the presence of nonvisceral or visceral metastases and the 3-year and 5-year OS rates for nonvisceral and visceral metastases were 67.1% [62.2-72.4%, 95% CI] and 24.4% [20.0-29.7%, 95% CI], 37.7% [27.5-51.9%, 95% CI] and 22.4% [14.0-35.8%, 95% CI], respectively. The median OS was also higher in patients with nonvisceral metastases and was 26.5 [17.6-38.9, 95% CI] and 17.3 [15.5-20.6, 95% CI] months, respectively. Our study revealed a statistically significant increase in OS and median OS in patients with IMDC unfavorable prognosis with non-visceral metastases (p<0.0001).

Thus, a statistically significant negative impact of visceral metastases on survival rates was found in mRCC patients in all IMDC prognosis groups.

We searched for the influence of the most important prognostic factors in patients with favorable and unfavorable prognosis based on the Cox proportional hazards model.

Table 3.18 shows that based on this model, in the single factor analysis, metastasis type, metastasectomy, visceral metastases and bone metastases influenced OS rates in mRCC patients with favorable prognosis according to IMDC, while in the multivariate analysis, gender, visceral metastases and alkaline phosphatase level were additional influential prognostic factors.

Table 3.18 – Cox proportional hazards model of the effect on survival rates in a subgroup of mRCC patients with a favorable prognosis according to IMDC (N=226)

Signs		Favorable outlook			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Gender	male female	0.5 (0.2÷1.4)	0.20	0.2 (0.1÷0.8)	0.02
Localization of metastases	1, 2, 3	1.4 (0.7÷2.9)	0.39	1.2 (0.5÷2.6)	0.66
Degree of differentiation	G 1, 2, 3	1.1 (0.6÷2.0)	0.65	1.2 (0.6÷2.3)	0.55
Type of metastasis	synchronous metachronous	0.3 (0.1÷0.9)	0.04	0.3 (0.1÷1.0)	0.04
Number metastases	solitary single multiple	1.1 (0.6÷1.9)	0.72	0.9 (0.3÷2.7)	0.82
Number of organs metastatic	one, two three or more	1.2 (0.7÷2.0)	0.47	1.0 (0.4÷2.5)	0.94

Continuation of Table 3.18

Signs		Favorable outlook			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Visceral and nonvisceral metastases		1.3 (0.9÷1.8)	<0.001	1.3 (0.7÷1.9)	<0.001
Metastasectomy	metastasectomy	0.4 (0.1÷0.9)	0.01	05 (0.2÷1.2)	0.01
Bones	0, 1	3.2 (1.4÷7.0)	0.005	7.0 (1.8÷26.4)	0.004
Lungs	0, 1	0.8 (0.4÷1.8)	0.58	0.8 (0.2÷2.5)	0.67
Liver	0, 1	1.6 (0.6÷4.8)	0.36	3.4 (0.7÷16.7)	0.13
Brain	0, 1	2.1 (0.5÷8.9)	0.3	1.0 (0.1÷7.3)	0.98
Lymph nodes	0, 1	0.7 (0.3÷1.9)	0.47	0.8 (0.2÷3.4)	0.74
Alkaline phosphatase	norm CF>ULN	1.0 (0.4÷2.4)	0.96	0.2 (0.1÷0.7)	0.01
LDH	norm >ULN	1.1 (0.5÷2.8)	0.76	0.5 (0.2÷1.4)	0.16

Table 3.19 shows that, based on this model, in a single-factor analysis, the degree of differentiation, type and number of metastases, performance of CN and metastasectomy, presence of visceral metastases, presence of liver and lymph node metastases, and levels of alkaline phosphate, LDH, and ESR influenced the OS in patients with mRCC of poor prognosis according to IMDC. In multivariate analysis, the degree of differentiation, the type and number of metastases, the performance of HE and metastasectomy, and the presence of visceral metastases were influential.

Table 3.19 – Cox proportional hazards model of the effect on survival rates in a subgroup of mRCC patients of unfavorable prognosis according to IMDC (N=403)

Signs		Unfavorable prognosis			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Gender	male female	0.8 (0.6÷1.0)	0.11	0.8 (0.6÷1.0)	0.10
Localization of metastases	1, 2, 3	1.0 (0.8÷1.2)	0.80	1.0 (0.8÷1.2)	0.78
Degree of differentiation	G 1, 2, 3	2.4 (1.9÷3.1)	<0.001	1.9 (1.5÷2.4)	<0.001
Type of metastasis	synchronous metachronous	0.6 (0.5÷0.7)	<0.001	0.6 (0.4÷0.7)	<0.001
Number metastases	solitary single multiple	2.4 (1.8÷3.1)	<0.001	1.8 (1.3÷2.5)	<0.001
Number of organs metastatic	one, two three or more	1.3 (1.1÷1.5)	<0.001	0.9 (0.7÷1.2)	0.55
CN	CN (±)	1.4 (0.9÷1.8)	<0.001	1.2 (0.9÷1.6)	<0.001
Metastasectomy	metastasectomy (±)	1.2 (1.0÷1.7)	0.001	1.0 (0.7÷1.6)	<0.001
Visceral and non-visceral. metastases		1.3 (0.9÷1.5)	<0.001	1.1 (0.9÷1.6)	<0.001
Bones	0, 1	1.2 (0.9÷1.4)	0.16	1.0 (0.7÷1.5)	0.83
Lungs	0, 1	1.2 (1.0÷1.5)	0.09	0.8 (0.6÷1.1)	0.12
Liver	0, 1	1.7 (1.3÷2.2)	<0.001	1.2 (0.8÷1.7)	0.47
Brain	0, 1	1.1 (0.7÷1.8)	0.59	1.3 (0.8÷2.2)	0.27
Lymph nodes	0, 1	1.5 (1.2÷1.8)	<0.001	1.3 (1.0÷1.7)	0.10
Alkaline phosphatase	norm CF>ULN	1.4 (1.1÷1.7)	0.003	0.8 (0.6÷1.1)	0.20

Continuation of Table 3.19

Signs		Unfavorable prognosis			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
LDH	norm >ULN	1.4 (1.1÷1.8)	0.002	1.2 (0.9÷1.6)	0.27
ESR	norm >ULN	1.9 (1.5÷2.4)	<0.001	1.1 (0.8÷1.4)	0.72

Table 3.20 shows that, based on this model, in the single-factor analysis, the type of metastases, number of metastases, number of affected organs, presence of bone metastases, and alkaline phosphate level influenced PFS in patients with a favorable prognosis according to IMDC mRCC. In multivariate analysis, the type of metastases and the presence of brain metastases were influential.

Table 3.20 – Cox proportional hazards model of the effect on PFS scores in a subgroup of mRCC patients with a favorable prognosis according to IMDC (N=226)

Signs		Favorable outlook			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Gender	male female	0.9 (0.5÷1.4)	0.51	1.2 (0.7÷2.1)	0.46
Localization of metastases	1, 2, 3	1.1 (0.8÷1.7)	0.56	1.2 (0.8÷1.8)	0.48
Degree of differentiation	G 1, 2, 3	1.1 (0.8÷1.4)	0.73	1.1 (0.8÷1.6)	0.43
Type of metastasis	synchronous metachronous	2.2 (0.9÷5.5)	0.08	2.9 (1.1÷7.7)	0.03

Continuation of Table 3.20

Signs		Favorable outlook			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Number metastases	solitary single multiple	1.7 (1.2÷2.3)	<0.001	1.5 (0.9÷2.5)	0.15
Number of organs metastatic	one, two three or more	1.4 (1.1÷1.9)	0.007	0.8 (0.5÷1.3)	0.38
Bones	0, 1	2.1 (1.3÷3.2)	<0.001	1.6 (0.8÷3.1)	0.18
Lungs	0, 1	1.1 (0.7÷1.8)	0.53	1.3 (0.7÷2.3)	0.46
Liver	0, 1	1.7 (0.9÷3.0)	0.08	1.6 (0.7÷3.7)	0.28
Brain	0, 1	2.0 (0.9÷4.7)	0.09	3.1 (1.1÷8.9)	0.03
Lymph nodes	0, 1	1.1 (0.7÷1.8)	0.6	1.1 (0.6÷2.2)	0.69
Alkaline phosphatase	norm CF>ULN	1.9 (1.3÷3.0)	0.002	1.3 (0.7÷2.3)	0.35
LDH	norm >ULN	1.4 (0.9÷2.2)	0.18	0.6 (0.3÷1.1)	0.09
ESR	norm >ULN	1.7 (1.1÷2.6)	0.01	1.0 (0.6÷1.8)	0.86

Table 3.21 shows that, based on this model, in the single-factor analysis, the degree of differentiation, number of metastases, number of organs with metastases, presence of liver and lymph node metastases, and levels of alkaline phosphate, LDH, and sedimentation influenced PFS in IMDC-positive mRCC patients. Multivariate analysis showed the influence of differentiation degree, number of metastases and lymph node involvement as factors affecting the PFS in IMDC patients with mRCC.

Table 3.21 – Cox proportional hazards model of the effect on PFS scores in the IMDC poor prognosis subgroup of mRCC patients (N=403)

Signs		Unfavorable prognosis			
		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Gender	male female	0.8 (0.6÷1.0)	0.07	0.8 (0.6÷1.0)	0.07
Localization of metastases	1, 2, 3	1.0 (0.8÷1.2)	0.98	1.0 (0.8÷1.3)	0.75
Degree of differentiation	G 1, 2, 3	2.1 (1.7÷2.7)	<0.001	1.7 (1.4÷2.2)	<0.001
Type of metastasis	synchronous metachronous	1.0 (0.8÷1.2)	0.74	1.1 (0.9÷1.4)	0.43
Number metastases	solitary single multiple	2.2 (1.7÷2.9)	<0.001	1.8 (1.3÷2.4)	<0.001
Number of organs metastatic	one, two three or more	1.4 (1.2÷1.6)	<0.001	0.9 (0.7÷1.2)	0.58
Bones	0, 1	1.2 (1.0÷1.5)	0.09	1.1 (0.8÷1.5)	0.63
Lungs	0, 1	1.2 (0.9÷1.5)	0.19	0.7 (0.6÷1.0)	0.06
Liver	0, 1	1.9 (1.4÷2.4)	<0.001	1.3 (0.9÷1.9)	0.21
Brain	0, 1	1.3 (0.8÷1.9)	0.30	1.2 (0.8÷2.1)	0.38
Lymph nodes	0, 1	1.5 (1.2÷1.9)	<0.001	1.3 (1.0÷1.8)	0.04
Alkaline phosphatase	norm CF>ULN	1.4 (1.1÷1.7)	0.003	0.8 (0.6÷1.0)	0.06
LDH	norm >ULN	1.5 (1.2÷1.9)	<0.001	1.2 (0.9÷1.6)	0.25
ESR	norm >ULN	2.0 (1.5÷2.5)	<0.001	1.1 (0.8÷1.5)	0.46

Thus, based on our study, we have identified various prognostic factors affecting the OS and PFS in mRCC patients with favorable, intermediate, or unfavorable prognosis according to the IMDC scale.

3.6 Duration of recurrence-free period as a prognostic factor in patients with metastatic renal cell cancer

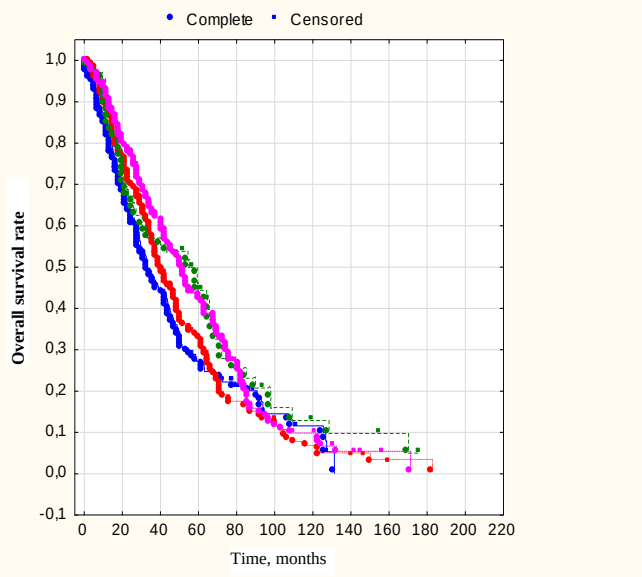
In our study, we examined the recurrence-free period (RFP) groups and evaluated prognostic factors affecting survival rates in mRCC patients. A total of 578 patients who were initially operated for localized renal cancer were included in the study. Depending on the duration of the RFP in this category, the patients were distributed into 4 groups.

Thus, the number of patients with a RFP of up to 12 months was 174 (30.1%), and 176 (30.4%) for a period of 1 to 3 years, 67 (11.6%) for 3 to 5 years, and 161 (27.9%) for more than 5 years, respectively, as shown in Table 3.22. Thus, about 60% of mRCC patients had a RFP of up to 3 years.

Table 3.22 – Distribution of patients depending on the time of RFP

RFP	Number of patients	HR
0-12 months.	174 (30.1)	–
1-3 yrs.	176 (30.4)	0.93 (0.73-1.19, p=0.565)
3 to 5 years old	67 (11.6)	0.73 (0.53-1.02, p=0.069)
over 5 years	161 (27.9)	0.78 (0.61-0.99, p=0.042)

As can be seen in Figure 3.23, the OS rates are directly related to the duration of the RFP and the 3-year and 5-year OS rates of patients were 46.2±1.5% and 27.8±1.4%, 59.5±1.6% and 32.9±1.6%, 57.6±1.6% and 44.4±1.6%, 66.8±1.6% and 42.1±1.6%, respectively. Median OS was 32, 40, 53, and 56 months, respectively.



p=0,012

Figure 3.23 – Comparison of Kaplan-Meier curves of OS indicators of mRCC patients (N=578) depending on the time of RFP

Thus, the study revealed a statistically significant increase in OS and median OS in mRCC patients with a RFP of more than 3 years in subgroups 3 and 4 (p=0.012).

We also looked in a multivariate analysis at factors affecting the duration of RFP in 578 mRCC patients.

Table 3.23 shows that in all recurrence -free periods, the degree of tumor differentiation according to Fuhrman in mRCC patients had a statistically significant effect on survival rates.

Table 3.23 – Cox proportional hazards model of the effect on OS rates in the overall cohort of mRCC patients in the recurrence-free groups (N=578)

Indicators		Number of patients	Single-factor	Multifactorial
Gender	men	410 (70.9)	–	–
	women	168 (29.1)	0.90 (0.73-1.10, p=0.306)	0.78 (0.63-0.96, p=0.021)

Continuation of Table 3.23

Indicators		Number of patients	Single-factor	Multifactorial
Age	18-44	24 (4.2)	–	–
	45-59	213 (36.9)	0.52 (0.34-0.81, p=0.004)	0.59 (0.38-0.93, p=0.022)
	60-74	288 (49.8)	0.69 (0.45-1.06, p=0.086)	0.73 (0.47-1.13, p=0.157)
	over 75	53 (9.2)	0.85 (0.52-1.41, p=0.534)	0.76 (0.46-1.27, p=0.296)
Histology	Clear-cell	529 (91.5)	–	–
	non-clear-cell	49 (8.5)	1.91 (1.38-2.63, p<0.001)	1.43 (1.02-2.01, p=0.038)
Grade of tumor	Grade1	166 (28.7)	–	–
	Grade2	237 (41.0)	1.77 (1.41-2.23, p<0.001)	1.60 (1.23-2.08, p<0.001)
	Grade3	175 (30.3)	2.52 (1.97-3.23, p<0.001)	2.18 (1.59-3.00, p<0.001)

Table 3.24 shows that in the study conducted in the RFP group up to 12 months in mRCC patients, the degree of tumor differentiation according to Fuhrman had a statistically significant effect on survival rates.

Table 3.24 – Cox proportional hazards model of the effect on OB outcomes of mRCC patients in the RFP group up to 12 months (N=174)

Factors	Gradations	Number of patients	Single-factor	Multifactorial
Gender	men	124 (71.3)	–	–
	women	50 (28.7)	0.89 (0.60-1.32, p=0.563)	0.74 (0.48-1.15, p=0.185)
Age	18-44	8 (4.6)	–	–
	45-59	68 (39.1)	0.42 (0.20-0.90, p=0.026)	0.70 (0.32-1.53, p=0.367)

Continuation of Table 3.24

Factors	Gradations	Number of patients	Single-factor	Multifactorial
	60-74	85 (48.9)	0.61 (0.29-1.27, p=0.185)	1.00 (0.47-2.12, p=0.991)
	over 75	13 (7.5)	0.60 (0.24-1.50, p=0.276)	0.66 (0.25-1.74, p=0.404)
Histology	clear-cell	147 (84.5)	–	–
	non- clear-cell	27 (15.5)	1.60 (1.00-2.57, p=0.051)	1.44 (0.87-2.40, p=0.156)
Grade	Grade 1	13 (7.5)	–	–
	Grade 2	56 (32.2)	2.61 (1.25-5.46, p=0.011)	2.06 (0.95-4.48, p=0.068)
	Grade 3	105 (60.3)	3.58 (1.77-7.25, p<0.001)	2.72 (1.26-5.90, p=0.011)

Table 3.25 shows that in the study conducted in the 1 to 3 years RFP group of mRCC patients, the degree of tumor differentiation according to Fuhrman had a statistically significant effect on survival rates.

Table 3.25 – Cox proportional hazards model of the effect on OS outcomes of mRCC patients in the 1 to 3 year RFP group (N=176)

Factors	Gradations	Number of patients	Single-factor	Multifactorial
Gender	men	124 (70.5)	-	-
	women	52 (29.5)	0.98 (0.68-1.40, p=0.909)	1.18 (0.81-1.74, p=0.388)
Age	18-44	8 (4.5)	–	–
	45-59	71 (40.3)	0.47 (0.23-1.00, p=0.049)	0.41 (0.19-0.88, p=0.022)
	60-74	83 (47.2)	0.53 (0.26-1.12, p=0.096)	0.40 (0.19-0.87, p=0.021)
	over 75	14 (8.0)	0.73 (0.30-1.76, p=0.482)	0.46 (0.19-1.14, p=0.094)

Continuation of Table 3.25

Factors	Gradations	Number of patients	Single-factor	Multifactorial
Histology	clear-cell	168 (95.5)	–	–
	non- clear-cell	8 (4.5)	2.31 (1.12-4.76, p=0.023)	1.50 (0.70-3.22, p=0.298)
Grade	Grade 1	22 (12.5)	–	–
	Grade 2	99 (56.2)	2.91 (1.66-5.13, p<0.001)	2.18 (1.18-4.02, p=0.013)
	Grade 3	55 (31.2)	4.67 (2.52-8.63, p<0.001)	2.75 (1.41-5.38, p=0.003)

Table 3.26 shows that in the study conducted in the 3 to 5 year group of mRCC patients, no factor had a statistically significant effect on survival rates.

Table 3.26 – Cox proportional hazards model of the effect on OS outcomes of mRCC patients in the 3 to 5 year RFP group (N=67)

Factors	Gradations	Number of patients	Single-factor	Multifactorial
Gender	men	52 (77.6)	–	–
	women	15 (22.4)	0.77 (0.38-1.55, p=0.464)	0.75 (0.34-1.65, p=0.476)
Age	18-44	3 (4.5)	–	–
	45-59	24 (35.8)	0.77 (0.22-2.66, p=0.676)	0.57 (0.16-2.07, p=0.393)
	60-74	34 (50.7)	1.23 (0.37-4.14, p=0.735)	0.68 (0.18-2.52, p=0.564)
	over 75	6 (9.0)	1.20 (0.23-6.16, p=0.826)	0.60 (0.10-3.62, p=0.575)
Histology	clear-cell	63 (94.0)	–	–
	non- clear-cell	4 (6.0)	2.16 (0.66-7.04, p=0.203)	1.95 (0.48-7.98, p=0.352)

Continuation of Table 3.26

Factors	Gradations	Number of patients	Single-factor	Multifactorial
Grade	Grade 1	24 (35.8)	–	–
	Grade 2	35 (52.2)	1.62 (0.87-3.02, p=0.125)	1.32 (0.67-2.59, p=0.427)
	Grade 3	8 (11.9)	2.26 (0.80-6.39, p=0.125)	1.97 (0.59-6.55, p=0.270)

Table 3.27 shows that in the study conducted in the group of mRCC patients with more than 5 years of RFP , the degree of tumor differentiation according to Fuhrman had a statistically significant effect on survival rates.

Table 3.27 – Cox proportional hazards model of the effect on OB outcomes of mRCC patients in the RFP group over 5 years (N=161)

Factors	Gradations	Number of patients	Single-factor	Multifactorial
Gender	men	110 (68.3)	–	–
	women	51 (31.7)	0.91 (0.63-1.31, p=0.616)	0.86 (0.57-1.28, p=0.453)
Age	18-44	5 (3.1)	–	–
	45-59	50 (31.1)	0.64 (0.23-1.80, p=0.396)	0.99 (0.33-3.00, p=0.986)
Age	60-74	86 (53.4)	0.84 (0.31-2.31, p=0.739)	1.24 (0.43-3.62, p=0.691)
	over 75	20 (12.4)	1.21 (0.41-3.56, p=0.731)	1.74 (0.53-5.73, p=0.365)
Histology	clear-cell	151 (93.8)	–	–
	non- clear-cell	10 (6.2)	2.10 (1.06-4.14, p=0.033)	1.45 (0.67-3.17, p=0.348)
Grade	Grade 1	107 (66.5)	–	–
	Grade 2	47 (29.2)	1.73 (1.17-2.54, p=0.005)	1.61 (1.03-2.52, p=0.035)
	Grade 3	7 (4.3)	1.99 (0.86-4.59, p=0.106)	1.95 (0.73-5.18, p=0.182)

Thus, in all RFP in mRCC patients, the degree of tumor differentiation according to Fuhrman had a statistically significant effect on survival rates. In our study we evaluated the influence of prognostic factors in each of the 4 mRCC groups and obtained the following results. Thus, in the groups of up to 1 year, from 1 to 3 years and in the group where RFP is more than 5 years old, the degree of tumor differentiation according to Fuhrman had a statistically significant influence on survival rates. In the study of the 3 groups with 3 to 5 years of RFP, none of the factors had a statistically significant effect on survival rates.

Conclusion

The influence of various clinical, morphologic, and laboratory factors on survival rates in mRCC patients, which are either already included in known prognostic models or are considered as potential prognostic factors, was analyzed.

In this study, IMDC prognosis groups should be taken into account in the clinical characteristics of prognosis in mRCC patients, which is directly related to survival rates in mRCC patients. Meanwhile, sex, age, and renal tumor localization had no influence on the OS rates of mRCC patients. We compared our clinical, morphologic, and laboratory factors with IMDC prognostic indicators and obtained the following results.

When further studying the influence of tumor morphological characteristics on survival rates of mRCC patients, in contrast to the IMDC model in our study, histological subtype and the degree of tumor differentiation according to Fuhrman were the most important prognostic factors affecting survival rates in mRCC patients. When we examined additional laboratory parameters that would have a statistically significant impact on mRCC survival rates in the overall cohort of mRCC patients, alkaline phosphatase, lactate dehydrogenase, and ESR levels were statistically significant parameters in the single-factor analysis, but none of these parameters showed prognostic significance in the multivariate analysis.

For a large number of studied parameters our data correlate with the data of previous studies: for example, survival rates of patients depend on the level of hemoglobin, platelets, ESR, LDH, alkaline phosphate.

Our work revealed heterogeneity of the intermediate prognosis group of mRCC patients depending on the number of unfavorable factors. Patients with 1 prognostic factor had more frequent G1 tumors (13.2/6.2) and more favorable ECOG status. Laboratory parameters did not demonstrate statistically significant differences.

Interesting results were obtained after comparing the influence of factors on survival rates in IMDC prognostic groups in mRCC patients. In all groups, the factors listed below, which relate to the characteristics of the metastatic disease itself, were influential.

In our study, we showed that in patients with favorable prognosis in single-factor analysis, type of metastases, performance of metastasectomy, presence of visceral metastases, and presence of bone metastases influenced OS rates in patients with favorable prognosis by IMDC; in multivariate analysis, gender, presence of visceral metastases, and alkaline phosphatase level were additional influencing factors.

For patients with mRCC of intermediate prognosis, additional factors influencing the OS were also the degree of tumor differentiation, type and number of metastases, CN performance and presence of visceral metastases in the single- and multivariate analysis of the Cox proportional hazards model.

In patients with poor prognosis of mRCC, the degree of tumor differentiation, type and number of metastases, performance of CN and metastasectomy, presence of visceral metastases, presence of metastases to the liver and lymph nodes, as well as the level of alkaline phosphorus, LDH and ESR were additional prognostic factors in the single-factor analysis. In multivariate analysis, the degree of differentiation, type and number of metastases, performance of CN and metastasectomy, and presence of visceral metastases were influential.

Thus, it is very important in our opinion that when we studied patients with mRCC in different IMDC prognostic groups, we identified additional prognostic

factors that directly affected survival rates and this emphasizes that current prognostic models are incomplete.

When studying prognostic factors in the groups of mRCC patients with different RFP, the degree of tumor differentiation according to Fuhrman had a statistically significant influence on survival rates.

In view of the above data established in our study, we already made further assessment of treatment efficacy depending on our additional prognostic factors.

All known above factors have shown an impact on survival rates in patients with mRCC and are consistent with the literature data. However, close attention should be paid to the peculiarity of the metastatic disease itself, which is practically neglected in clinical trials with systemic therapy.

Thus, as a result of the study, in addition to prognostic factors according to IMDC, we have identified the following additional indicators influencing survival rates. The histological subtype and the degree of tumor differentiation according to Fuhrman were the most important prognostic factors influencing the survival rates in mRCC patients. We found a statistically significant difference in survival rates in mRCC patients of the intermediate prognosis group depending on the number of unfavorable factors. Also, our study established additional factors affecting survival rates in mRCC patients with favorable, intermediate and unfavorable prognosis.

In view of the above, it is highly relevant to define a new personalized model with the inclusion of our new prognostic factors.

Chapter 4
STUDY OF THE CHARACTERISTICS OF METASTATIC LESIONS AS A PROGNOSTIC, AFFECTING SURVIVAL RATES OF PATIENTS WITH METASTATIC RENAL CELL CANCER

To determine the characteristics of metastatic lesions, we analyzed the influence of localization and number of metastases on survival rates and therapy in mRCC patients.

4.1 Analysis of the metastatic lesion in metastatic renal-cell carcinoma and its impact on survival rates

4.1.1 Dependence of survival rates on the number of affected organs and localization of metastases

4.1.1.1 Dependence of survival rates of the number of organs affected

Our study showed that the majority of patients had 1 organ lesion in 39.4% of cases, as shown in Figure 4.1.

As can be seen in Figure 4.2, the OS rates were directly related to the number of organs affected and the 3-year and 5-year OS rates for 1 organ affected were 62.4±1.7% and 36.1±1.5%, two organs 56.1±1.7% and 27.0±1.5%, three organs 41.3±1.5% and 29.3±1.6% and four organs or more 58.8±1.5% and 31.1±1.4%, respectively. The median OS also differed among patients depending on the number of organs affected and was 48, 38, 29 and 41 months, respectively.

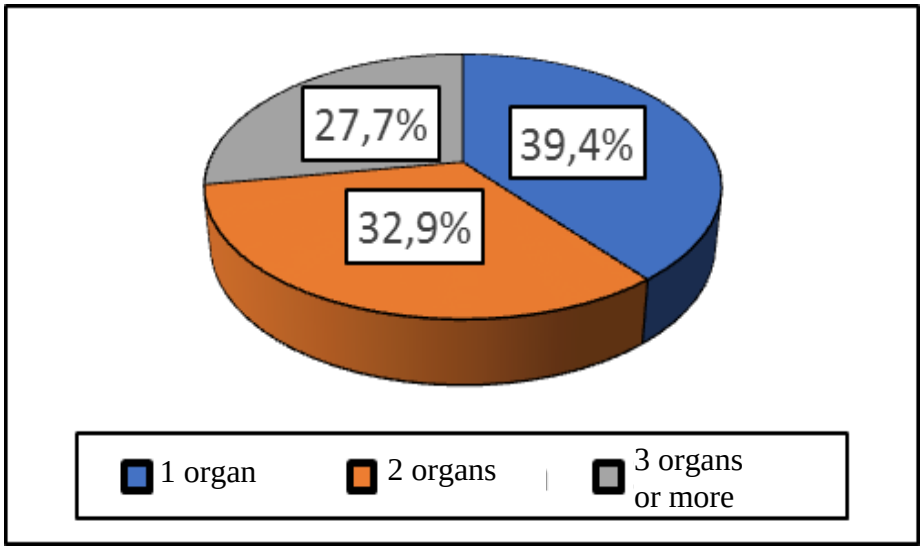
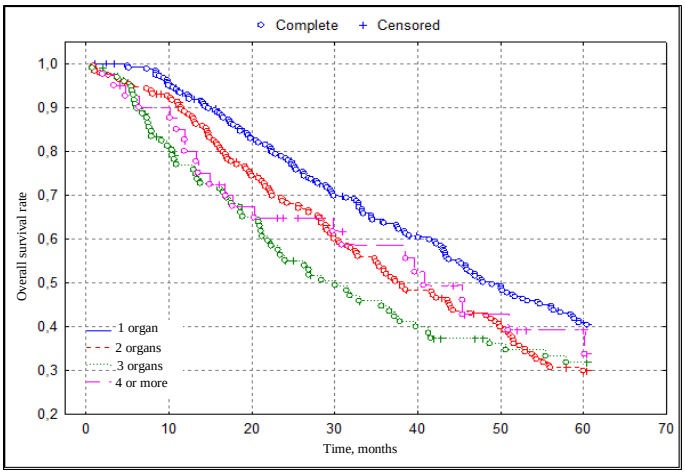


Figure 4.1 – Distribution of mRCC patients depending on the number of organs affected by metastases



p=0,0008

Figure 4.2 – Comparison of OB indicators of mRCC patients depending on the number of affected organs (N=981)

Thus, the study revealed statistically significant differences in OS and median OS depending on the number of affected organs (p=0.0008). At the same time, the OS indices are higher when one organ is affected. In addition, there were higher OS indices when four organs or more were affected as opposed to metastatic foci in two and three organs.

4.1.1.2 Dependence of survival rates from the localization of metastases

When evaluating the patients included in the study according to the localization of metastases, the most frequent metastases were identified in the lungs, bones and lymph nodes in 66.7%, 38.7% and 34% of cases, respectively (Figure 4.3).

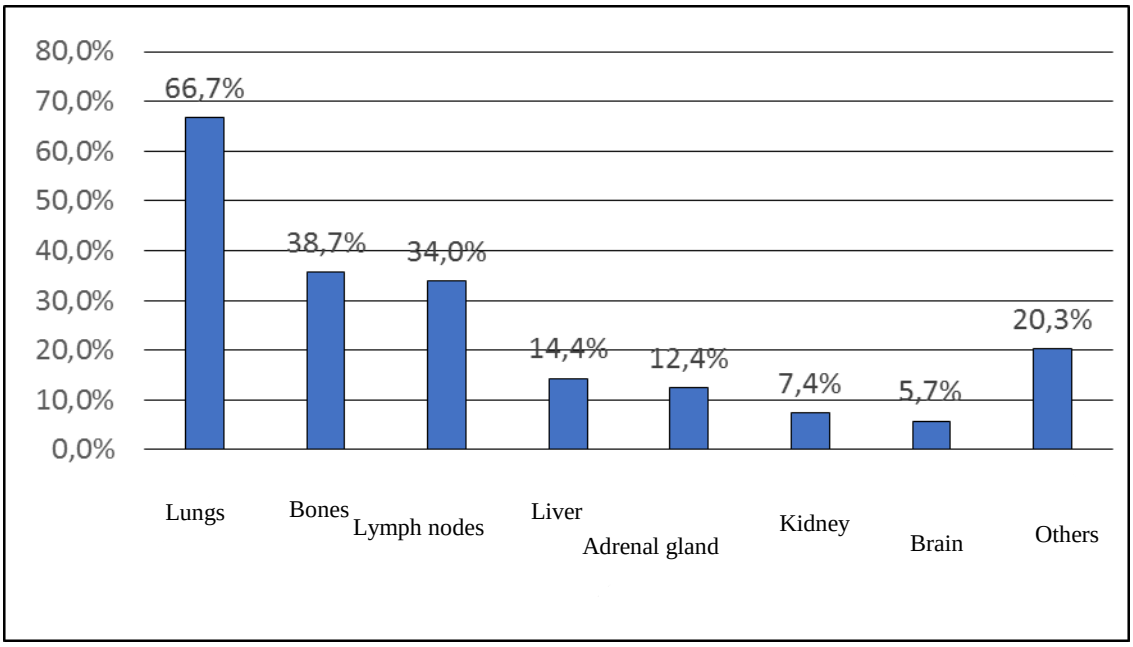


Figure 4.3 – Distribution of mRCC patients
by frequency of localization of metastases

As shown in Table 4.1, the most frequent combinations in mRCC patients with multi-organ metastatic lesions were as follows:

Table 4.1 – Distribution of mRCC patients depending on combinations of localizations of metastatic lesions

Localization	Number of cases	%
Lungs+lymph nodes	92	9.4
Bones+lungs	64	6.3
Bones+lungs+lymph nodes.	35	3.4

Continuation of Table 4.1

Localization	Number of cases	%
Lungs+other	31	3.1
Bone+lymph nodes	15	1.4
Lungs+liver	15	1.4
Bones+lungs+liver	14	1.3
Lungs+adrenal+lymph nodes	12	1.1
Lymph nodes+other	11	1.0
Bones+lungs+adrenal lungs.	11	1.0
Lungs+liver+lymph nodes	11	1.0

As in our study, in the work of C. Karacin et al. showed ≥2 sites of metastasis in 87.6% of patients [201].

Table 4.1 shows that the most frequent single organ lesions were lungs – 195 cases (19.5%), bones – 88 cases (8.7%), lymph nodes – 35 (3.5%), 18 patients (1.85%) had an isolated adrenal lesion, 11 (1.1%) patients had liver, 10 (1%) had isolated metastatic lesion of the contralateral kidney, 9 (0.9%) had isolated metastases to the brain and 2 women (0.2%) had ovarian lesions. Other localizations accounted for 32 cases (3.2%). In the work of T. Chandrasekar et al. associated liver, bone and/or brain metastases with poor outcomes in patients with mRCC [149, 150].

Further, for patients with 1 organ lesion (N=386), we compared the OS indices depending on the localization. In the work of D. Santini et al. metastatic lesion of one organ was detected in 8.1% of patients [158].

When evaluating the patients included in the study, bone metastases were identified in 350 (35.7%) patients (Table 4.2), with isolated metastases in 89 patients.

As shown in Figure 4.4, the 3-year and 5-year OS rates were 37.4±1.5% and 11.9±1.4%, respectively. The median OS of mRCC patients with isolated bone lesions was 27.9 months.

Table 4.2 – Distribution of mRCC patients depending on the presence or absence of bone metastases

Bone metastasis	Number of patients	HR
Bone metastasis (-)	631 (64.3)	–
Bone metastases (+)	350 (35.7)	1.40 (1.21-1.62, p<0.001)

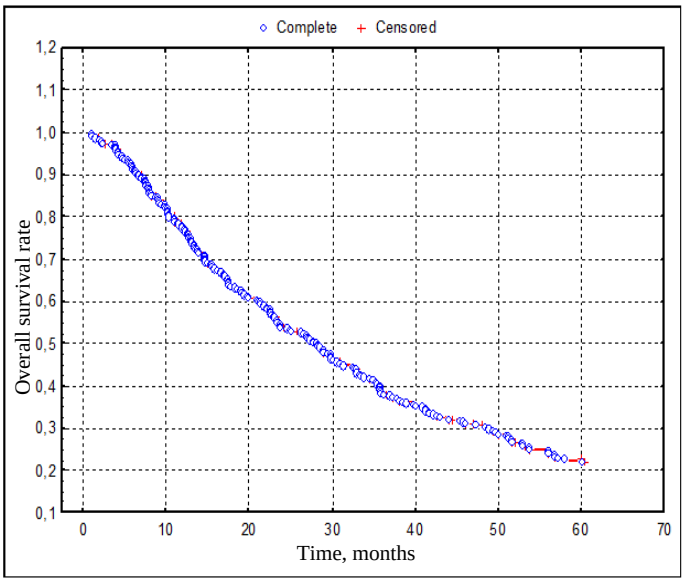


Figure 4.4 – Kaplan-Meier curve of OS indicators in patients with isolated bone lesions (N=89)

Lung metastases were detected in 655 (66.8%) patients, with isolated metastases in 191 patients.

In mRCC patients with isolated metastatic lung lesions, the 3-year and 5-year OS rates were 44.5±1.6% and 27.6±1.5%, respectively. The median OS in patients with isolated metastatic lung disease was 34.4 months (Table 4.3, Figure 4.5).

Table 4.3 – Distribution of mRCC patients depending on the presence or absence of lung metastases

Lung metastasis	Number of patients	HR
Lung metastases (-)	326 (33.2)	–
Lung metastases (+)	655 (66.8)	1.15 (0.99-1.33, p=0.069)

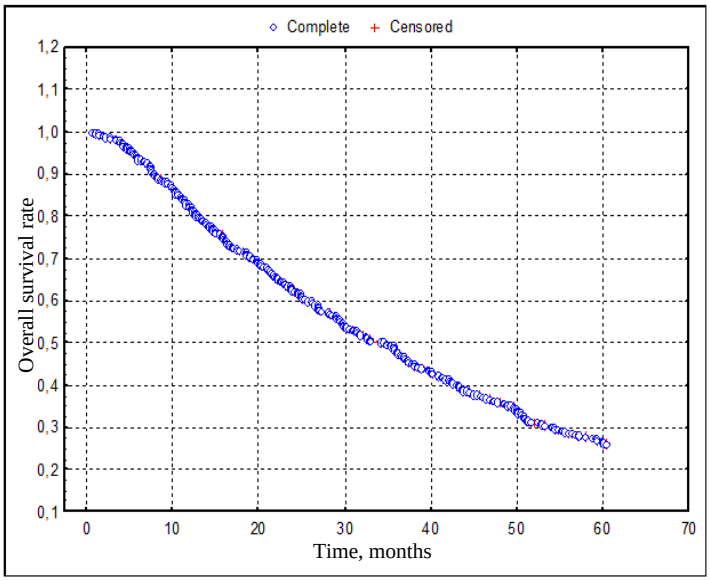


Figure 4.5 – Kaplan-Meier curves of OS indicators
in mRCC patients with isolated lung lesions (N=191)

Metastases to lymph nodes were detected in 332 (33.9%) patients, with isolated metastases in 34 patients.

Survival analysis showed that the 3-year and 5-year OS of mRCC patients with isolated metastatic lymph node involvement were 38.9±1.6% and 21.4±1.5%, respectively (Table 4.4, Figure 4.6). The median OS in patients with isolated metastatic lymph node involvement was 26.8 months.

Table 4.4 – Distribution of mRCC patients depending on the presence or absence of metastases to lymph nodes

Lymph nodes	Number of patients	HR
mts in lymph nodes (-)	649 (66.1)	–
mts in lymph nodes (+)	332 (33.9)	1.41 (1.22-1.64, p<0.001)

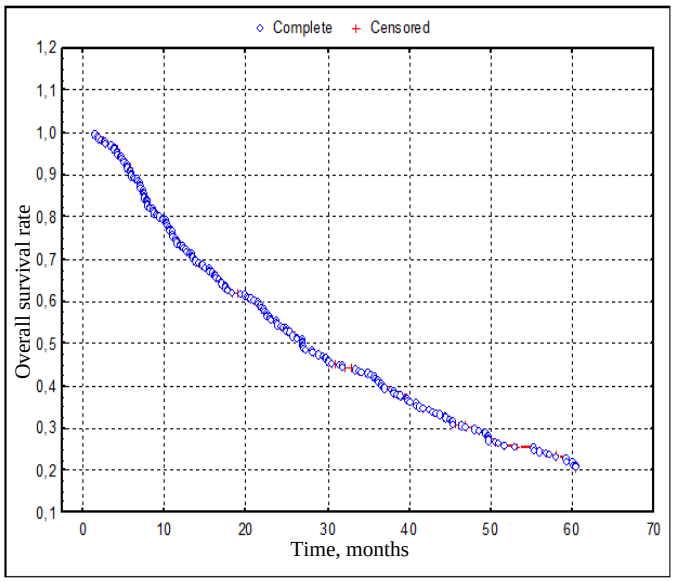


Figure 4.6 – Kaplan-Meier curves of OS indicators
in patients with isolated lymph node lesions (N=34)

Thus, there were statistically significant differences depending on the organ in which the isolated metastatic lesion was observed. There were lower OS in patients with mRCC with isolated metastases to bones and lungs.

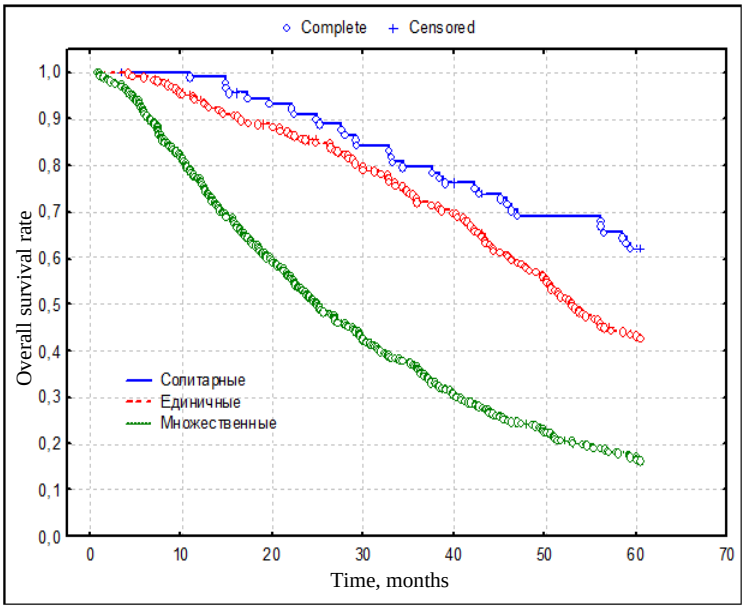
4.2 Dependence of survival rates on prevalence metastases and clinical and morphologic features of patients

By prevalence, metastases are divided into:

1. Solitary – one hearth.
2. Single – 2-3 metastases.
3. Multiple.

As can be seen in Figure 4.7, the OS rates are directly related to the number of metastases and the 3-year and 5-year OS rates of patients with solitary, single and multiple metastases were 80.7±1.6% and 56.1±1.4%, 72.5±1.7% and 38.3±1.6%, 33.5±1.7% and 13.8±1.3%, respectively. The median OV for solitary metastases was

not reached. Median OS of single and multiple metastases 52 and 24 months, respectively.



p<0,0001

Figure 4.7 – OS indices in patients with solitary, single and multiple metastases of RCC

Thus, the conducted study revealed statistically significant differences in the OS and median OS indices in mRCC patients depending on the number of metastases (p<0.0001). This indicator is an important factor for predicting the OS rates, which is consistent with the current literature data [40, 119, 160, 262].

Hemoglobin levels were lower in patients with multiple metastases, the best hemoglobin values were in patients with solitary metastases. At the same time, the levels of alkaline phosphate, LDH, ESR and platelet count in peripheral blood were higher in patients with multiple metastases. Interestingly, platelet count and LDH were lower in patients with single metastases compared to solitary metastases.

Thus, the number of metastases influenced not only survival rates but also clinical and laboratory parameters, which can be used to develop diagnostic criteria.

4.2.1 Analysis of clinical and morphologic features of metastatic lesions in patients with renal-cell cancer with solitary metastases

Ninety (9.2%) patients with solitary metastases of RCC were included in the study.

When patients were allocated according to the morphological characteristics of the tumor, the following results were obtained (Table 4.5).

Table 4.5 – Distribution of patients with solitary metastases of RCC depending on the localization and histological characteristics of the tumor

Histologic variant	GRADE	Metastases to bone, N	Lung metastases, N	Metastasis to the kidney	Metastasis to the adrenal gland	Metastasis to the liver	Metastasis to Lymph nodes	Metastasis into the brain	Other localizations of metastases
Clear-cell	1	4	4	0	5	4	0	1	8
	2	4	2	1	3	5	0	2	9
	3	5	1	6	2	5	1	5	7
Papillary	1	0	0	0	0	1	0	0	1
	2	0	0	1	0	1	1	0	0
	3	0	0	0	0	1	0	0	0
Chromophobic	1	0	0	1	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	0	0	0	0	0
Other	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	0	0	1	1	0	0	2

Table 4.5 shows that solitary metastases were described in all localizations included in the study in patients with squamous cell RCC, G1 (35 patients). The most

frequent metastatic lesion of a single organ was observed in the adrenal gland – 9 patients (25.7%). The contralateral kidney was frequently affected in the study – 6 cases (17.1), 4 cases – bone and lung (11.4% each), in 2 patients – liver (5.7%). Other localizations of metastases occurred in 10 patients.

A patent for the industrial design – scheme – algorithm for treatment of solitary metastases of renal cancer in bone was obtained (Figure 4.8).


РОССИЙСКАЯ ФЕДЕРАЦИЯ

ПАТЕНТ

НА ПРОМЫШЛЕННЫЙ ОБРАЗЕЦ

№ 111898

СХЕМА "АЛГОРИТМ ЛЕЧЕНИЯ СОЛИТАРНЫХ МЕТАСТАЗОВ РАКА ПОЧКИ В КОСТИ"

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Руководитель Федеральной службы по интеллектуальной собственности

Figure 4.8 – Design Patent Scheme

"Algorithm for the treatment of solitary renal cancer metastases to bone"

In patients with squamous cell RCC, G2 (32 cases), the most frequent were isolated lesions of the adrenal gland (6 cases – 18.7%), bones – 4 patients (12.5%), brain lesions were observed in 3 patients (9.3%), in 3 patients metastatic lesions were determined in the contralateral kidney (9.4%). Other localizations accounted for 17 cases.

In patients with clear cell RCC, G3 (15 cases), 5 (33.3%) patients metastasized to bone, 4 (26.7%) to the brain, and 2 (13.3%) patients had an isolated adrenal lesion. Other localizations accounted for 4 (26.7%) cases.

Non-small cell tumor variants accounted for 6 cases (6.7%), of which 3 were papillary cancer and 1 was chromophobe cancer. In 2 patients metastases were detected in the contralateral kidney, 1 case each with isolated involvement of lymph nodes and liver, and 2 patients with isolated metastases of other localizations.

In patients with solitary metastases of RCC, papillary cancer was more common in liver lesions.

Comparison of the frequency of organ involvement depending on the histologic variant and degree of differentiation revealed statistically significant differences only for lymph node involvement (Table 4.6). For other localizations of metastases in patients with solitary metastases of RCC no statistically significant differences were revealed ($p>0.05$).

Table 4.6 – Frequency of metastatic lesions of lymph nodes in patients with mRCC depending on the histological variant and degree of tumor differentiation

Histologic variant of RCC	Degree differentiations	Lymph nodes unaffected	The lymph nodes are affected
Clear-cell	1	35 (100.00%)	0 (0.00%)
Clear-cell	2	32 (100.00%)	0 (0.00%)
Clear-cell	3	14 (93.33%)	1 (6.67%)
Papillary	1	1 (100.00%)	0 (0.00%)
Papillary	2	2 (66.67%)	1 (33.33%)
Papillary	3	1 (100.00%)	0 (0.00%)
Chromophobic	1	1 (100.00%)	0 (0.00%)
Chromophobic	2	2 (100.00%)	0 (0.00%)
Chromophobic	3	0 (0.00%)	0 (0.00%)
		(chi-square 24.7441, df=12, p=.016083)	

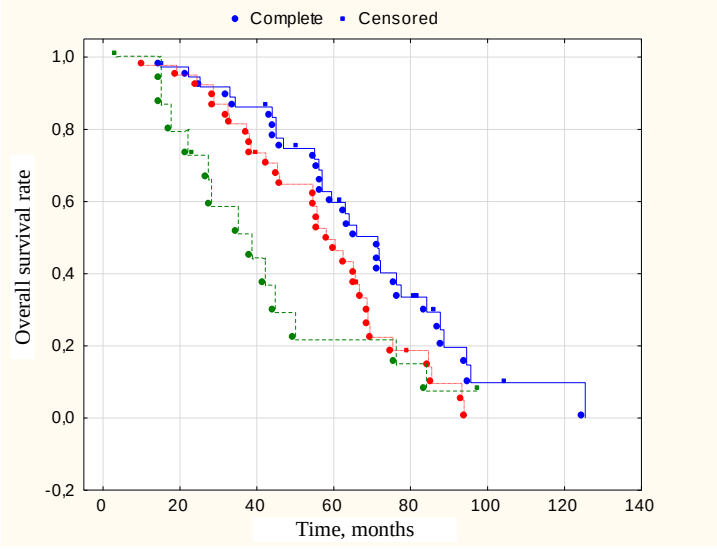
Table 4.6 shows that lymph node involvement in the group of solitary metastases of RCC was extremely rare, somewhat more frequent in the clear-cell variant, G3, and even more frequent in the papillary variant, G2.

When evaluating the patients with solitary metastases included in the study according to the degree of tumor differentiation, the patients were divided into 3 groups. Table 4.7 shows that G1 was detected in 37 (41.1%), G2 and G3 in 37 (41.1%) and 16 (17.8%) patients, respectively. Thus, G1 and G2 predominated in 37 (41.1%) patients each

Table 4.7 – Distribution of patients with solitary metastases of mRCC depending on the degree of tumor differentiation according to Fuhrman

Grade	Number of patients	HR
1	37 (41.1)	–
2	37 (41.1)	2.16 (1.26-3.69, p=0.005)
3	16 (17.8)	2.04 (1.04-3.97, p=0.037)

OB rates in patients with solitary metastases depending on the degree of tumor differentiation (Figure 4.9).



p=0,009

Figure 4.9 – Kaplan-Meier curves of OS indicators
in patients with solitary metastases of RCC
depending on the degree of tumor differentiation according to Fuhrman (N=90)

As shown in Figure 4.9, the OS rates directly depend on the degree of tumor differentiation according to Fuhrman and the 3- and 5-year OS rates of patients were 84.2±1.8% and 59.9±1.7%, 80.3±1.8% and 46.7±1.6%, 52.2±1.8% and 22.2±1.6%, respectively. The median OS also differed and was 63, 56 and 31 months at G1, G2 and G3, respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on the degree of tumor differentiation according to Fuhrman (p=0.009).

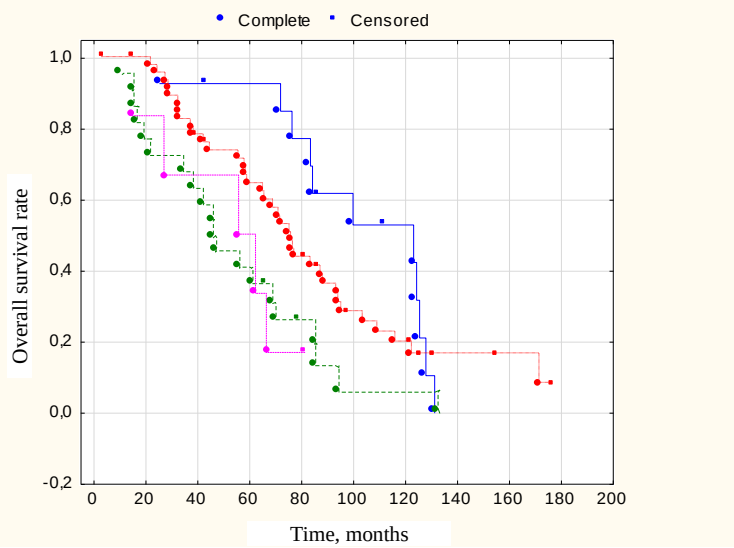
When evaluating the patients with solitary metastases of RCC included in the study according to ECOG status, Table 4.8 shows that patients with good somatic status ECOG 0-1 predominated in 69.9% of cases.

Table 4.8 – Distribution of patients with solitary metastases of mRCC depending on ECOG status

ECOG status	Number of patients	HR
ECOG0	14 (15.6)	–
ECOG1	48 (53.3)	1.41 (0.71-2.79, p=0.326)
ECOG2	22 (24.4)	2.96 (1.39-6.29, p=0.005)
ECOG3	6 (6.7)	3.43 (1.15-10.20, p=0.027)

OS rates in patients with solitary metastases of RCC depending on ECOG status (Figure 4.10).

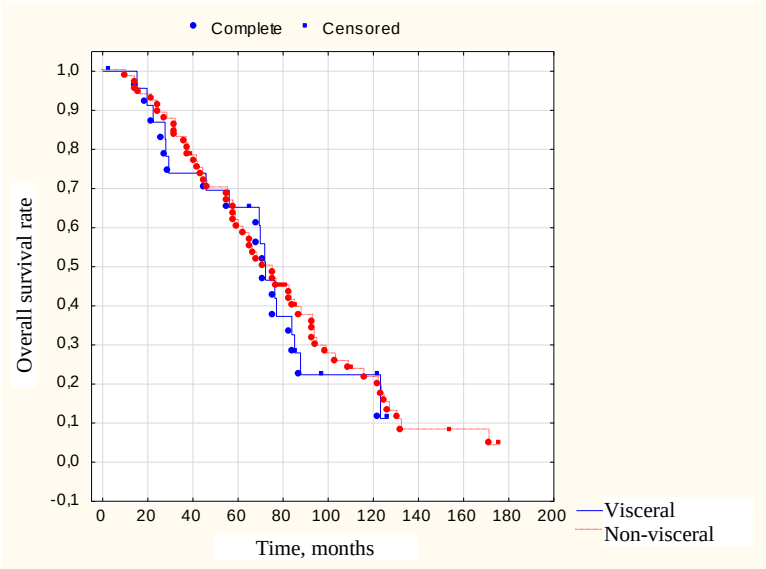
As we can see from Figure 4.10, the rates of OS depend on ECOG status and the rates of 3- and 5-year OS of RCC patients were 92.8±1.8% and 92.8±1.8%, 79.2±1.8% and 64.4±1.6%, 68.4±1.8% and 36.3±1.4%, 62.2±1.8% and 36.3±1.4%, respectively. The median OS also differed at ECOG0, 1, 2, 3 and was 93, 71, 46 and 59 months, respectively. Thus, the study revealed statistically significant differences in OS and median OS in patients with solitary metastases of RCC depending on ECOG status (p=0.002).



p=0,002

Figure 4.10 – Kaplan-Meier measures of OS in patients with solitary metastases of RCC depending on ECOG status (N=90)

The OS rates in patients with solitary visceral and non-visceral metastases of RCC are presented in Figure 4.11.



p=0,41

Figure 4.11 – Kaplan-Meier curves of OS indicators in patients with solitary nonvisceral/visceral metastases of RCC (N=90)

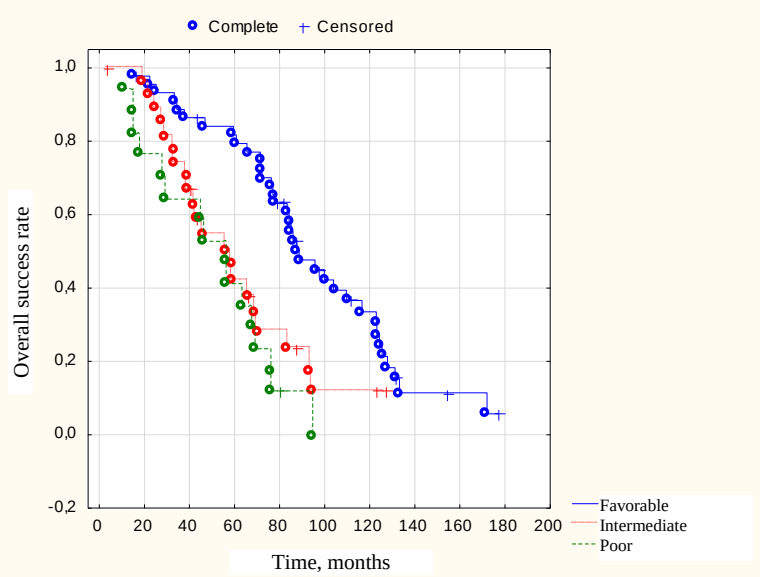
As shown in Figure 4.11 in patients with nonvisceral/visceral metastases of RCC, the 3- and 5-year OS rates were 82.3±1.8% and 60.1±1.6%, 74.7±1.8% to 65.4±1.6%, respectively. The median OS did not differ in the presence of nonvisceral/visceral metastases was 72 and 71 months, respectively. Thus, there was no statistically significant difference in OS and median OS in mRCC patients in the presence of solitary non-visceral/visceral metastases (p=0.41).

Although we consider separately the factors included in the IMDC prognostic model, we also evaluated survival rates in 3 prognostic groups in the overall cohort of patients with solitary metastases of RCC. When evaluating the RCC patients with solitary metastases included in the study according to the number of prognostic factors according to the IMDC classification, the patients were categorized into 3 groups. Table 4.9 shows that the number of mRCC patients with favorable prognosis was 45 (50.0%), intermediate and unfavorable prognosis 28 (31.1%) and 17 (18.9%) patients, respectively. Thus, more than 80% of patients were from favorable and intermediate prognosis groups according to IMDC.

Table 4.9 – Distribution of patients with solitary metastases of RCC depending on IMDC prognosis

IMDC Forecast	Number of patients	HR
Favorable	45 (50.0)	–
Intermediate	28 (31.1)	2.41 (1.36-4.27, p=0.003)
Poor	17 (18.9)	3.82 (2.01-7.26, p<0.001)

As can be seen from Figure 4.12, the survival rates directly depend on the prognosis according to the IMDC scale. Thus, in the favorable prognosis group the 3-year and 5-year OS of patients were 87.4±1.8% and 79.5±1.7%, in the intermediate prognosis group – 75.2±1.8% and 42.3±1.6%. And the OS rates in the poor prognosis group were 63.5±1.8% and 41.3±1.6, respectively. And the median OS in IMDC prognosis groups were 85, 58 and 57 months, respectively.



p<0,0001

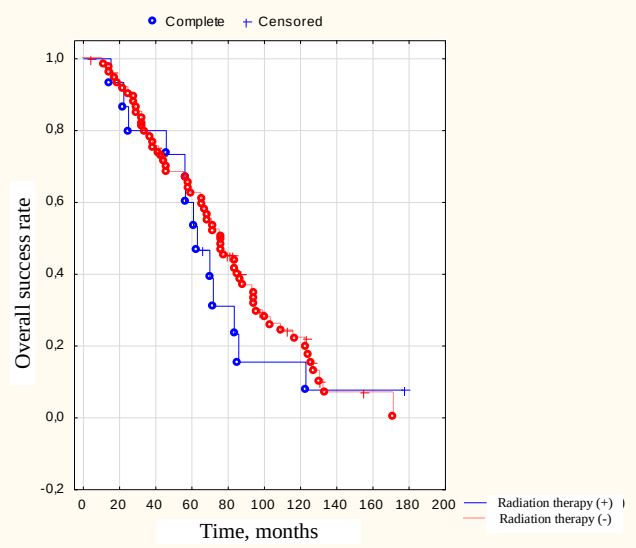
Figure 4.12 – Kaplan-Meier curves of OS indicators in patients with solitary metastases of RCC depending on IMDC prognosis (N=90)

Thus, the study revealed statistically significant differences in OS and median OS depending on IMDC prognosis in patients with solitary metastases of RCC (p<0.0001).

Survival analysis showed that the 3- and 5-year OS of patients with solitary metastases of RCC with and without radiation therapy were 80.2±1.8% and 53.3±1.6%, 79.5±1.8% and 62.5±1.6%, respectively. And the median OS was 61 and 77 months, respectively (Table 4.10, Figure 4.13). Thus, there is no advantage in the OS rates of radiation therapy in patients with solitary metastases of RCC (p=0.46).

Table 4.10 – Distribution of patients with solitary metastases of mRCC depending on the presence/absence of radiation therapy

Radiation therapy	Number of patients	HR
Radiation therapy (-)	75 (83.3)	–
Radiation therapy (+)	15 (16.7)	1.26 (0.69-2.32, p=0.451)

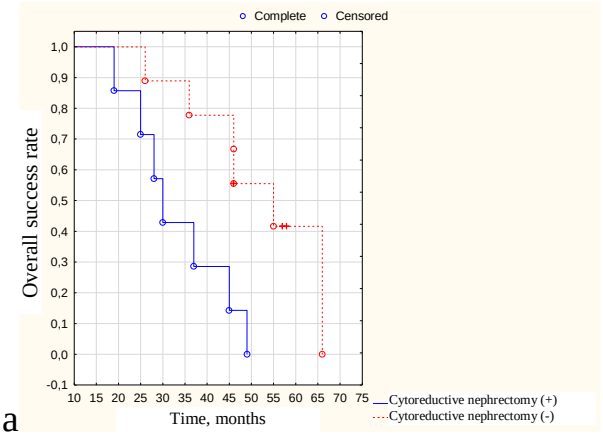


p=0,46

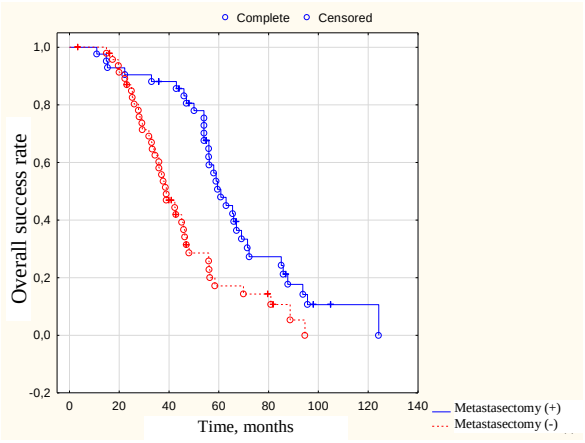
Figure 4.13 – Kaplan-Meier curves of patients' OS indicators with solitary metastases of RCC in the presence/absence of radiation therapy (N=90)

Survival rates were analyzed depending on CN and metastasectomy in patients with solitary metastases of RCC (Figure 4.14).

a



b



p=0,008 p=0,0007

a – depending on the presence/absence of OS;

b – depending on the presence/absence of metastasectomy (N=90).

Figure 4.14 – Kaplan-Meier curves of OS indicators in patients with solitary metastases of RCC

The analysis of the effect of cytoreductive surgeries on survival rates of patients with solitary metastases of mRCC patients showed the following peculiarities: CN had a significant effect on OS (p=0.008, Figure 14, a), as well as metastasectomy (p=0.0007, Figure 14, b). In patients with and without CN performed, the 3- and 5-year OS rates were 78.2±1.7% and 40.3±1.6%, 29.2±1.4% and 0%, respectively. The median OS also differed and was 55 and 30 months, respectively.

In patients with and without metastasectomy, the 3- and 5-year OS rates were 86.3,6±1.8% and 59.6±1.6%, 61.3±1.6% and 19.8±1.3%, respectively. The median OS in performing/not performing metastasectomy was 59 and 38 months, respectively.

Thus, in this study, the degree of tumor differentiation according to Fuhrman, performance of CN and metastasectomy were factors influencing the rates of OS in patients with solitary metastases of RCC.

Next, our study performed a single- and multivariate analysis of the influence of prognostic factors on the OS parameters in patients with solitary metastases of RCC (Table 4.11).

Table 4.11 – Cox proportional hazards model of the effect on OS in the group of patients with solitary metastases of RCC (N=90)

Factors	Gradations	Number sick	HR (single-factor)	HR (multivariate)
Gender	men	56 (62.2)	–	–
	women	34 (37.8)	0.92 (0.57-1.48, p=0.721)	0.66 (0.35-1.25, p=0.205)
Age	18-44	1 (1.1)	–	–
	45-59	35 (38.9)	0.75 (0.10-5.58, p=0.777)	0.24 (0.03-2.06, p=0.192)
	60-74	49 (54.4)	1.23 (0.17-8.98, p=0.841)	0.55 (0.07-4.66, p=0.584)
	over 75	5 (5.6)	4.61 (0.52-41.16, p=0.171)	1.99 (0.16-24.66, p=0.594)

Continuation of Table 4.11

Factors	Gradations	Number sick	HR (single-factor)	HR (multivariate)
Histological variant	clear-cell	82 (91.1)	–	–
	non- clear-cell	8 (8.9)	1.46 (0.67-3.22, p=0.342)	1.29 (0.49-3.36, p=0.605)
Degree of differentiation	1	37 (41.1)	–	–
	2	37 (41.1)	2.16 (1.26-3.69, p=0.005)	1.57 (0.76-3.24, p=0.226)
	3	16 (17.8)	2.04 (1.04-3.97, p=0.037)	2.69 (1.06-6.79, p=0.037)
Type of metastasis	synchronous	16 (17.8)	–	–
	metachronous	74 (82.2)	0.71 (0.38-1.31, p=0.275)	1.53 (0.69-3.42, p=0.298)
Bones	bone mts (-)	77 (85.6)	–	–
	bone mts (+)	13 (14.4)	1.55 (0.81-2.98, p=0.189)	1.79 (0.72-4.43, p=0.212)
Lungs	mts to the lungs (-)	83 (92.2)	–	–
	mts to the lungs (+)	7 (7.8)	0.42 (0.17-1.04, p=0.061)	0.53 (0.18-1.57, p=0.254)
Liver	mts to the liver (-)	85 (94.4)	–	–
	mts to the liver (+)	5 (5.6)	0.82 (0.30-2.26, p=0.702)	2.70 (0.45-16.27, p=0.278)
Lymph nodes	mts in lymph nodes (-)	88 (97.8)	–	–
	mts in lymph nodes (+)	2 (2.2)	0.51 (0.07-3.69, p=0.506)	0.31 (0.03-2.96, p=0.308)
Brain	brain mts (-)	82 (91.1)	–	–
	brain mts (+)	8 (8.9)	3.65 (1.72-7.74, p=0.001)	16.05 (3.92-65.68, p<0.001)
Hemoglobin	Hemoglobin's normal	80 (88.9)	–	–
	Anemia	10 (11.1)	0.67 (0.27-1.66, p=0.386)	0.61 (0.21-1.72, p=0.348)

Continuation of Table 4.11

Factors	Gradations	Number sick	HR (single-factor)	HR (multivariate)
Alkaline phosphatase	alkaline phosphorus is normal	74 (82.2)	–	–
	alkaline phosphorus is above normal	16 (17.8)	0.93 (0.49-1.78, p=0.825)	1.47 (0.45-4.80, p=0.525)
LDH	LDH is normal	69 (76.7)	–	–
	LDH is above normal	21 (23.3)	1.48 (0.85-2.57, p=0.164)	1.86 (0.84-4.09, p=0.124)
Platelets	Platelets are normal	69 (76.7)	–	–
	Thrombocytosis	10 (11.1)	0.66 (0.28-1.54, p=0.339)	0.19 (0.03-1.36, p=0.098)
	Thrombocytopenia	11 (12.2)	1.94 (0.94-3.99, p=0.073)	0.38 (0.11-1.27, p=0.117)
ECOG	ECOG0	14 (15.6)	–	–
	ECOG1	48 (53.3)	1.41 (0.71-2.79, p=0.326)	2.43 (0.91-6.49, p=0.078)
	ECOG2	22 (24.4)	2.96 (1.39-6.29, p=0.005)	3.21 (1.05-9.83, p=0.042)
	ECOG3	6 (6.7)	3.43 (1.15-10.20, p=0.027)	1.42 (0.23-8.88, p=0.705)
Metastasectomy	metastasectomy (-)	55 (61.1)	–	–
	metastasectomy (+)	35 (38.9)	0.57 (0.35-0.92, p=0.021)	0.88 (0.44-1.76, p=0.719)
	radiation therapy (-)	75 (83.3)	–	–
	radiation therapy (+)	15 (16.7)	1.26 (0.69-2.32, p=0.451)	0.85 (0.37-1.96, p=0.706)

Table 4.11 shows that in the single-factor Cox analysis, Fuhrman tumor differentiation, brain metastasis and metastasectomy were the factors influencing the RR in patients with solitary metastases of RCC. In Cox multivariate analysis, the degree of tumor differentiation according to Fuhrman and brain metastasis were the factors influencing the RR in patients with solitary metastases of RCC.

Thus, the study of survival rates in patients with solitary metastases of RCC in multivariate analysis showed the influence of the degree of tumor differentiation according to Fuhrman, as well as the presence of brain metastases.

4.2.2 Analysis of clinical and morphologic features metastatic lesions in patients with renal-cell cancer with single metastases

The study included 252 (25.7%) patients with single metastases of mRCC, with single organ involvement in 180 patients. Light-cell cancer was verified in 234 patients, papillary cancer in 10 patients, chromophobe cancer in 4 patients, and other variants in 4 patients of mRCC. According to the degree of differentiation, G1 90 (35.7%) and G2 94 (37.3%) patients and patients with favorable and intermediate prognosis 96 (38.1%) and 105 (41.7%) patients were also predominant, respectively.

The following results were obtained depending on morphological characteristics (Table 4.12).

Table 4.12 – Distribution of IRCC patients with single metastases depending on the localization and histological characteristics of the tumor

Histologic variant	GRADE	Metastasis in bone, N	Metastasis into the lungs, N	Metastasis in the kidney	Metastasis to the adrenal gland	Metastasis into the liver	Metastasis to Lymph nodes	Metastasis into the brain	Other localizations of metastases
Clear-cell	1	27	57	5	9	2	10	1	8
	2	33	47	5	6	1	11	3	15
	3	17	30	2	2	0	5	4	2
Papillary	1	0	2	0	0	1	0	0	0
	2	2	1	0	0	0	0	0	1
	3	2	0	0	0	0	1	0	1

Continuation of Table 4.12

Histologic variant	GRADE	Metastasis in bone, N	Metastasis into the lungs, N	Metastasis in the kidney	Metastasis to the adrenal gland	Metastasis into the liver	Metastasis to Lymph nodes	Metastasis into the brain	Other localizations of metastases
Chromophobic	1	0	1	0	0	0	0	0	0
	2	1	1	0	0	1	1	0	0
	3	1	0	0	0	0	0	0	0
Other	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
	3	0	2	0	0	0	0	0	2

Table 4.12 shows that in single metastases of RCC, the luminal variant was dominant, with G2 and G1 tumor metastases being more frequent, but it was noteworthy that non-small cell subtypes were increasingly common. Metastases to the kidneys, adrenal glands, and brain were always of the non-small cell subtype. Liver involvement was relatively rare with frequent lymph node involvement. Bones and lungs remained the dominant localization, papillary and chromophobe variants were characteristic for them, where in these localizations were determined exclusively of the clear-cell subtype.

In patients with single metastases of clear cell RCC, isolated lung (39 patients, 45.3%) or bone (11 patients, 12.8%) lesions were most frequently observed at G1 (86 patients). Interestingly, combined lesions of these localizations were the third most frequent (6 patients, 6.9%). In addition, 9 patients had combined lesions of internal organs and bones, and another 9 had combined lesions of lungs and other internal organs. Isolated lymph node involvement was relatively common (5 patients, 5.8%). Isolated adrenal lesions were not found in this group, but 5 cases were found in combination with other organs. The liver was infrequently affected in patients with single metastases and only in combination (4 patients). Brain metastases were found

in one patient in combination with lung lesions. Contralateral kidney involvement was detected in 6 patients, but again in combination.

In patients with clear cell RCC, isolated lung (29 patients – 32.9%) or bone (26 patients – 29.5%) lesions were most frequently observed at G2 (88 cases), isolated adrenal gland lesion was determined in the third place (7 patients, 7.9%). Combined lesion of bones and internal organs was revealed in 7 patients (7,9%), and in 11 patients (12,5%) combined lesion of lungs and other organs. Liver damage was noted in 5 patients (isolated in two and combined in three). Adrenal gland involvement isolated or in combination was detected in 4 cases (4.5%). Combined lesion of the brain was found in 2 patients. Involvement of the contralateral kidney was noted in 5 patients with combined organ involvement.

In patients with clear cell RCC, the same trend was observed at G3 (60 cases): isolated lung and bone lesions were leading by a significant margin – 26 (43.3%) and 13 (21.7%) cases, respectively. Isolated metastatic lesion of lymph nodes was detected in 4 patients (6.7%). Metastases in the brain were observed in 4 patients (6.7%). Liver involvement was rare, in combination with involvement of other organs in 5 patients (8.3%). Metastases to the adrenal glands and contralateral kidney were detected in only 2 patients.

Non-small cell variants of RCC accounted for 18 cases (7.1%), the incidence and localization of metastases are presented in Table 4.13.

Table 4.13 shows that the comparison of the frequency of organ damage in patients with single metastases of non-small cell RCC depending on the histological variant and degree of differentiation revealed statistically significant differences for adrenal, liver and other localizations. For other localizations of metastases in patients with single metastases of RCC no statistically significant differences were revealed ($p>0.05$).

Table 4.13 – Frequency of occurrence of localizations of single metastases of different histological variants of non-small cell RCC

Localizations metastasis of RCC	Papillary cancer			Chromophobe cancer			Other
	G1	G2	G3	G1	G2	G3	G3
Bones		1	2		1	1	
Lymph nodes		1					
Liver		1	1				
Lungs	2			1			2
Bones+lungs		1					
Lungs+lymph nodes					1		
Adrenal+other							1
Liver+other	1						1

A patent for the industrial design – scheme – algorithm for treatment of single kidney cancer metastases in bone was obtained (Figure 4.15).


РОССИЙСКАЯ ФЕДЕРАЦИЯ

ПАТЕНТ

НА ПРОМЫШЛЕННЫЙ ОБРАЗЕЦ

№ 113723

СХЕМА-АЛГОРИТМ ЛЕЧЕНИЯ ЕДИНИЧНЫХ МЕТАСТАЗОВ РАКА ПОЧКИ В КОСТЯХ

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Руководитель Федеральной службы по интеллектуальной собственности

Г.П. Ивлиев

Figure 4.15 – Design Patent Scheme

"Algorithm for the treatment of single renal cancer metastases to bone"

Table 4.14 shows that the adrenal glands were never affected in papillary and chromophobe variants of RCC, and rarely in clear cell variants of RCC (somewhat more often in G1 tumors). For metastases to the liver, a decrease in the degree of tumor differentiation was associated with an increased risk of affecting this organ; in papillary cancer, liver metastases were detected in one third of patients. Other histologic variants of RCC statistically significantly often gave metastases to the liver and adrenal glands in 25% of cases.

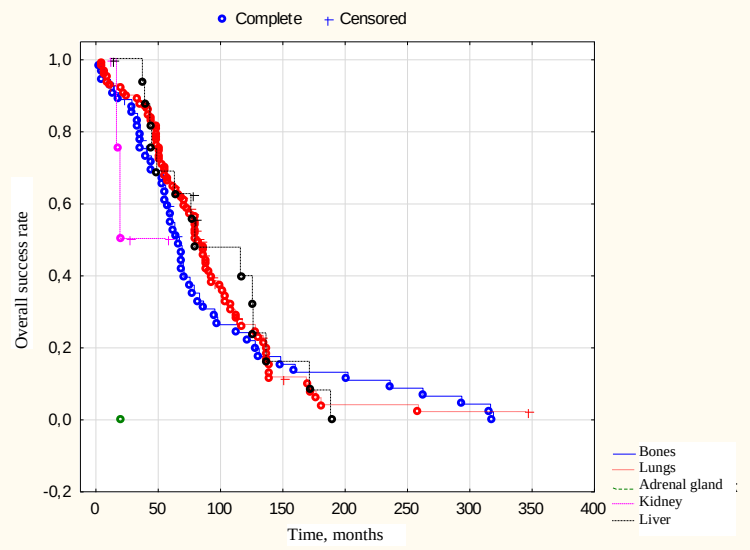
Table 4.14 – Frequency of metastatic organ involvement in patients with single metastases of RCC depending on histologic variant and degree of differentiation (only statistically significant differences)

Histologic variant of RCC	Degree of differentiation	The adrenal glands are not affected	The adrenal glands are affected	The liver's unaffected	The liver's affected
Clear-cell	1	81 94.19%	5 5.81%	82 95.35	4 6.45%
	2	85 96.59%	3 3.41%	83 94.32%	5 5.68%
	3	58 96.67%	2 3.33%	55 91.67%	5 8.33%
Papillary	1	3 100.00%	0 0.00%	2 66.67%	1 33.33%
	2	4 100.00%	0 0.00%	3 75.00%	1 25.00%
	3	3 100.00%	0 0.00%	2 66.67%	1 33.33%
Chromophobic	1	1 100.00%	0 0.00%	1 100.00%	0 0.00%
	2	2 100.00%	0 0.00%	2 100.00%	0 0.00%
	3	1 100.00%	0 0.00%	1 100.00%	0 0.00%

Continuation of Table 4.14

Histologic variant of RCC	Degree of differentiation	The adrenal glands are not affected	The adrenal glands are affected	The liver's unaffected	The liver is affected
Other	1	0	0	0	0
	2	0.00%	0.00%	0.00%	0.00%
	3	3 75.00%	1 25.00%	3 (75%)	1 (25%)
		chi-cad 28.0725, df=17, p=.044098.		*chi-square 28.3 df=17, p=.041*	

The OS rates in patients with single metastases of RCC depending on the localization of metastases in one organ are presented in Figure 4.16.



p=0,188

Figure 4.16 – Kaplan-Meier curves of OS indicators in patients with single metastases of RCC depending on the localization of metastases (N=252)

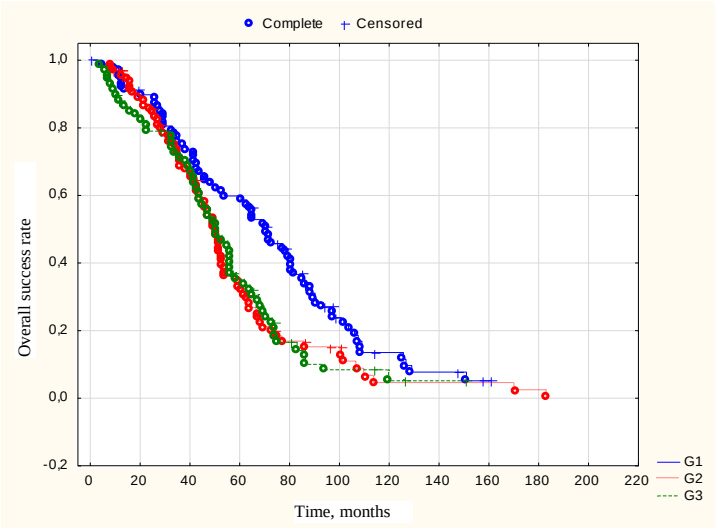
In patients with nonvisceral metastases, the 3- and 5-year OS rates were 78.2±1.7% and 43.8±1.5% for bone metastases, respectively. In patients with visceral metastases, the 3- and 5-year OS rates ranged from 90.6±1.8% to 44.5±1.5%, respectively.

When evaluating patients with single metastases of RCC included in the study according to the degree of tumor differentiation, the patients were distributed into 3 groups. Table 4.15 shows that G1 was detected in 90 (35.7%), G2 and G3 in 94 (37.3%) and 68 (27.0%) patients, respectively. Thus, our study was dominated by patients with tumor differentiation grade G1 and G2 in 73% of cases.

Table 4.15 – Distribution of patients with sporadic metastases of mRCC depending on the degree of tumor differentiation according to Fuhrman

Degree of differentiation	Number of patients	HR
Grade1	90 (35.7)	–
Grade2	94 (37.3)	1.58 (1.14-2.19, p=0.006)
Grade3	68 (27.0)	1.59 (1.12-2.26, p=0.009)

The OS rates in patients with single metastases of RCC depending on the degree of tumor differentiation are presented in Figure 4.17.



p=0,01

Figure 4.17 – Kaplan-Meier curves of OS indicators
in patients with single metastases of RCC
depending on the degree of tumor differentiation according to Fuhrman (N=252)

As can be seen from Figure 4.17, the OS rates directly depend on the degree of tumor differentiation according to Fuhrman and the 3- and 5-year OS rates of the patients were 87.5±1.8% and 58.7±1.7%, 73.4±1.8% and 36.2±1.4%, 70.2±1.8% and 31.7±1.4%, respectively. The median OS also differed and was 71, 49 and 50 months at G1, G2 and G3, respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on the degree of tumor differentiation according to Fuhrman in patients with single metastases of RCC (p=0.01).

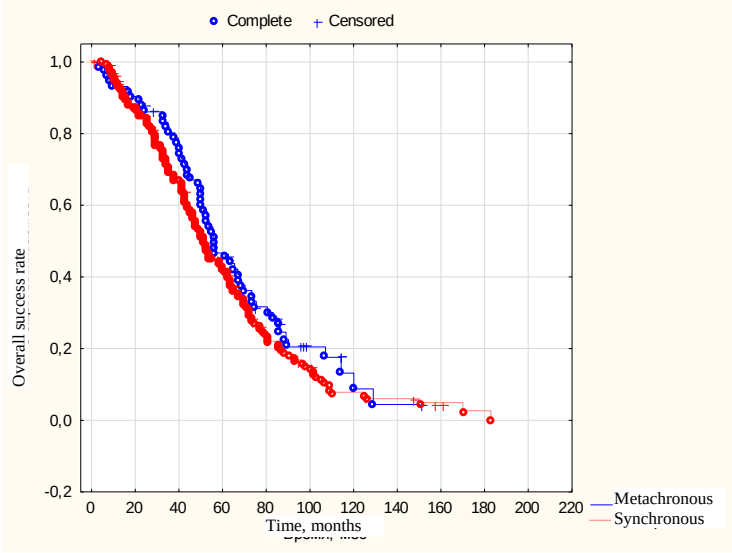
When evaluating patients with single metastases of RCC included in the study according to the type of metastases, patients with metachronous metastases predominated in 71% of cases (Table 4.16).

Table 4.16 – Distribution of patients with solitary metastases of mRCC depending on the type of metastases

Type of metastasis	Number of patients	HR
Synchronous	73 (29.0)	–
Metachronous	179 (71.0)	1.21 (0.89-1.65, p=0.216)

The rates of OS in patients with single metastases of RCC depending on the time of metastases appearance are presented in Figure 4.18.

Figure 4.18 shows that the 3- and 5-year OS rates of patients with metachronous and synchronous metastases were 81.4±1.8% and 45.3±1.7%, 70.83±1.8% and 41.4±1.6%, respectively. The median OS was 57 and 54 months, respectively. Thus, patients with single synchronous and metachronous metastases of RCC showed no statistically significant differences in OS and median OS (p=0.21).



p=0,21

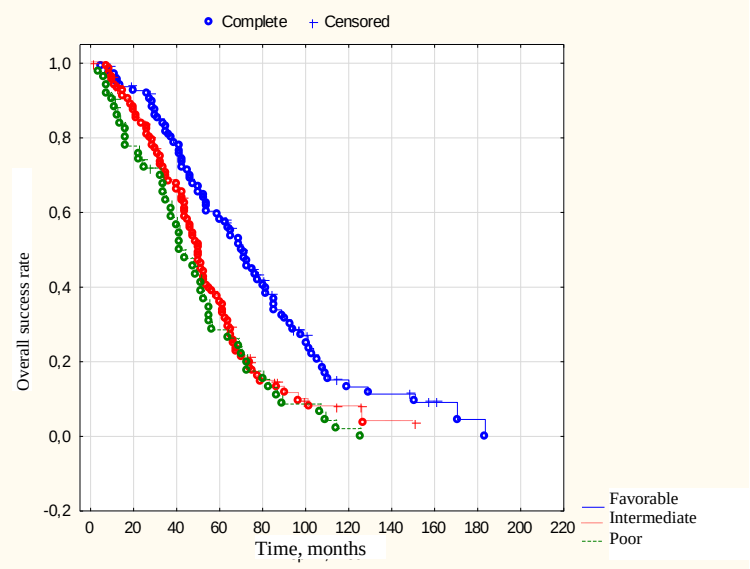
Figure 4.18 – Kaplan-Meier curves of OS indicators in patients with single metastases depending on the type of metastases (N=252)

Although we consider separately the factors included in the IMDC prognostic model, we also evaluated survival rates in 3 prognostic groups in the overall cohort of patients with single metastases of RCC. When evaluating patients with single metastases included in the study according to the number of prognostic factors according to the IMDC classification, patients were categorized into 3 groups. Table 4.17 shows that the number of mRCC patients with favorable prognosis was 96 (38.1%), intermediate and unfavorable prognosis 105 (41.7%) and 51 (20.2%) patients, respectively. Thus, 78% of patients were from the groups of favorable and intermediate prognosis according to IMDS.

Table 4.17 – Distribution of mRCC patients with single RCC metastases according to IMDC prognosis

IMDC Forecast	Number of patients	HR
Favorable	96 (38.1)	–
Intermediate	105 (41.7)	1.76 (1.28-2.42, p=0.001)
Poor	51 (20.2)	2.12 (1.47-3.07, p<0.001)

The OS rates in patients with single metastases of RCC depending on IMDC prognosis are presented in Figure 4.19.



p<0.0001

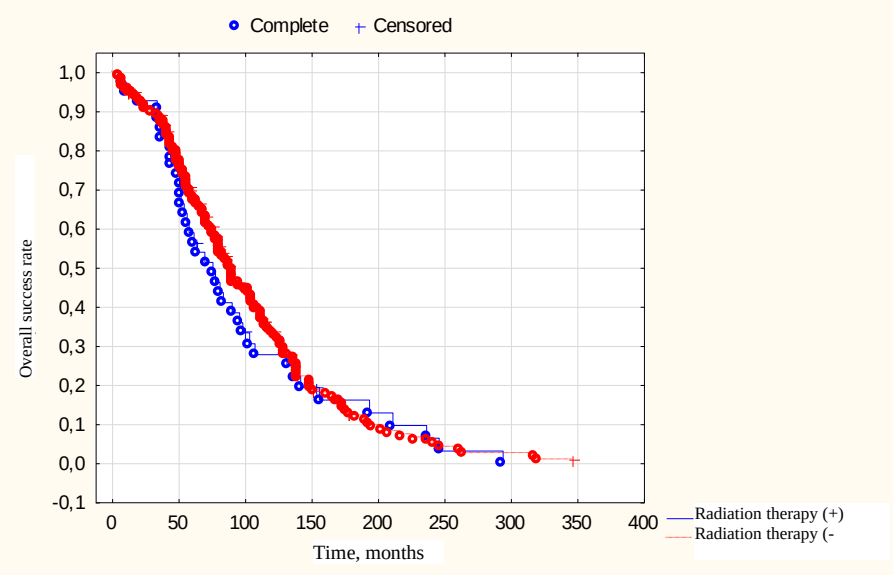
Figure 4.19 – Kaplan-Meier curves of OS indicators in patients with single metastases of RCC depending on IMDC prognosis (N=252)

As can be seen from Figure 4.19, the survival rates directly depend on the prognosis according to the IMDC scale. Thus, in the group of mRCC patients with favorable prognosis the 3-year and 5-year OS of patients made 81.5±1.8% and 58.5±1.7%, in the group of intermediate prognosis – 78.6±1.8% and 34.5±1.4%, respectively. And the OS rates in the poor prognosis group were 68.5±1.7% and 28.8±1.3%. Meanwhile, the median OS in the IMDC prognosis groups also differed and was 68, 46 and 40 months, respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on IMDC prognosis in patients with single metastases of RCC (p<0.0001).

Radiation therapy in patients with single metastases of mRCC is summarized in Table 4.18 and Figure 4.20.

Table 4.18 – Distribution of patients with sporadic metastases of RCC depending on the provision/absence of radiation therapy

Radiation therapy	Number of patients	HR
Radiation therapy (-)	210 (83.3)	–
Radiation therapy (+)	42 (16.7)	1.10 (0.77-1.57, p=0.593)



p=0,59

Figure 4.20 – Kaplan-Meier curves of patients OS indicators with sporadic metastases of RCC in the absence of radiation therapy (N=252)

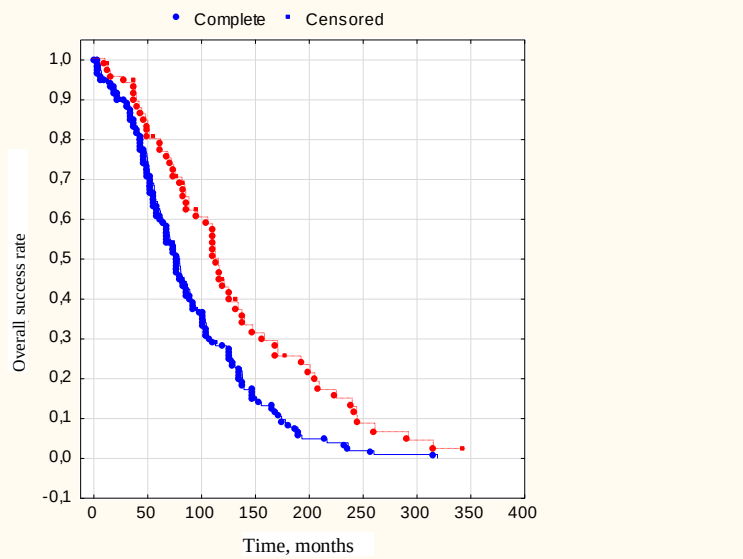
Analysis of survival rates demonstrated that the 3- and 5-year OS rates of mRCC patients with single RCC metastases with and without radiation therapy were 84.7±1.8% and 43.8±1.6%, 83.9±1.8% and 36.6±1.6%, respectively. Meanwhile, the median OS was 69 and 82 months, respectively. Thus, there is no advantage in the OS rates of radiation therapy in patients with single metastases of RCC (p=0.59).

In the evaluation of mRCC patients with single metastases included in the study, it was found that metastasectomy was performed in 68 (27%) patients (Table 4.19).

Table 4.19 – Distribution of patients with single metastases of mRCC depending on the performance/absence of metastasectomy

Metastasectomy	Number of patients	HR
Metastasectomy (-)	184 (73.0)	–
Metastasectomy (+)	68 (27.0)	0.67 (0.49-0.91, p=0.011)

Metastasectomy in patients with single metastases of mRCC is presented in Figure 4.21.



p=0,011

Figure 4.21 – Kaplan-Meier curves of patients OS indicators with single metastases of RCC When metastasectomy is performed/not performed (N=252)

The presented Kaplan-Meier curves demonstrated that the 3- and 5-year OS rates of patients with single RCC metastases with and without metastasectomy were 93.2±1.6% and 56.6±1.6%, 86.3±1.6% and 37.4±1.6%, respectively. Meanwhile, the median OS was also higher in RCC patients when metastasectomy was performed and was 112 and 74 months, respectively. Thus, the study showed significant differences in OS and median OS depending on metastasectomy in patients with single metastases of RCC (p=0.011).

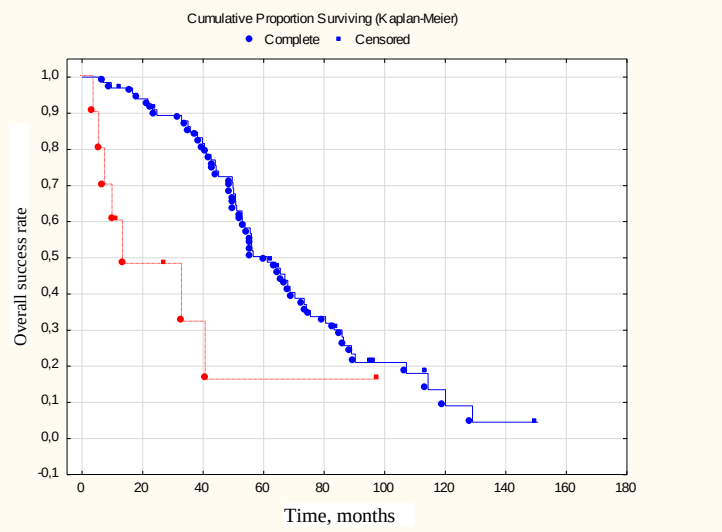
When evaluating patients with single metastases of RCC included in the study, it was found that CN was performed in an overwhelming 96.4% of patients (Table 4.20).

Table 4.20 – Distribution of patients with sporadic metastases of RCC depending on the presence/absence of CN

NE	Number of patients	HR
CN (+)	243 (96.4)	–
CN (-)	9 (3.6)	1.82 (0.75-4.44, p=0.186)

HE in patients with single metastases of mRCC is presented in Figure 4.22.

Survival analysis showed that the 3- and 5-year OS of patients with single metastases of RCC with and without CN were 84.8±1.8% and 50.3±1.6%, 33.8±1.4% and 17.4±1.3%, respectively. Meanwhile, the median OS was also higher in RCC patients when NE was performed and was 56 and 13 months, respectively. Thus, the study showed significant differences in OS and median OS depending on the performance of CN in patients with single metastases of RCC (p=0.004).



p=0,004

Figure 4.22 – Kaplan-Meier curves of patients' AO indicators with single metastases of RCC in the absence of CN (N=252)

Thus, the degree of tumor differentiation according to Fuhrman, performance of CN and metastasectomy were factors influencing the rates of OS in patients with single metastases of RCC.

Next, we performed a single- and multivariate analysis of the influence of prognostic factors on OS parameters in patients with single metastases of RCC (Table 4.21).

Table 4.21 – Cox proportional hazards model of the effect on OS rates in the group of patients with single metastases of RCC (N=262)

Factors	Gradations	All of them	HR (single-factor)	HR (multivariate)
Gender	men	172 (68.3)	–	–
	women	80 (31.7)	0.95 (0.71-1.28, p=0.735)	0.69 (0.49-0.98, p=0.040)
Age	18-44	9 (3.6)	–	–
	45-59	106 (42.1)	0.88 (0.41-1.91, p=0.752)	1.23 (0.49-3.13, p=0.658)
Age	60-74	110 (43.7)	1.13 (0.52-2.43, p=0.763)	1.43 (0.57-3.61, p=0.448)
	over 75	27 (10.7)	1.43 (0.61-3.34, p=0.413)	1.77 (0.64-4.88, p=0.269)
Localization	on the right	121 (48.0)	–	–
	on the left	127 (50.4)	1.01 (0.77-1.33, p=0.937)	1.05 (0.77-1.42, p=0.769)
	bilateral	4 (1.6)	0.71 (0.23-2.25, p=0.565)	0.72 (0.20-2.66, p=0.624)
CN	CN (+)	243 (96.4)	–	–
	CN (-).	9 (3.6)	1.82 (0.75-4.44, p=0.186)	0.75 (0.23-2.44, p=0.632)
Histological variant	clear-cell	234 (92.9)	–	–
	non- lear-cell	18 (7.1)	1.37 (0.78-2.41, p=0.268)	1.05 (0.55-1.98, p=0.886)

Continuation of Table 4.21

Factors	Gradations	All of them	HR (single-factor)	HR (multivariate)
Degree differentiations	Grade1	90 (35.7)	–	–
	Grade2	94 (37.3)	1.58 (1.14-2.19, p=0.006)	1.17 (0.79-1.73, p=0.431)
	Grade3	68 (27.0)	1.59 (1.12-2.26, p=0.009)	1.14 (0.72-1.80, p=0.575)
Type of metastasis	synchronous	73 (29.0)	–	–
	metachronous	179 (71.0)	1.21 (0.89-1.65, p=0.216)	1.67 (1.15-2.43, p=0.007)
Bones	bone mts (-)	169 (67.1)	–	–
	bone mts (+)	83 (32.9)	1.37 (1.03-1.82, p=0.033)	0.80 (0.45-1.44, p=0.459)
Lungs	mts to the lungs (-)	115 (45.6)	–	–
	mts to the lungs (+)	137 (54.4)	0.65 (0.50-0.86, p=0.002)	0.61 (0.36-1.04, p=0.067)
Liver	mts to the liver (-)	234 (92.9)	–	–
	mts to the liver (+)	18 (7.1)	1.53 (0.90-2.60, p=0.113)	0.72 (0.34-1.52, p=0.389)
Lymph nodes	mts in lymph nodes (-)	224 (88.9)	–	–
	mts in lymph nodes (+)	28 (11.1)	0.95 (0.60-1.50, p=0.832)	0.87 (0.49-1.52, p=0.618)
Brain	brain mts (-)	244 (96.8)	–	–
	brain mts (+)	8 (3.2)	0.60 (0.27-1.36, p=0.222)	0.34 (0.12-0.96, p=0.041)
Hemoglobin	hemoglobin is normal	199 (79.0)	–	–
	anemia	53 (21.0)	1.93 (1.39-2.67, p<0.001)	1.32 (0.88-1.97, p=0.182)
Alkaline phosphatase	alkaline phosphorus is normal	180 (71.4)	–	–
	alkaline phosphorus is elevated	72 (28.6)	1.48 (1.10-1.98, p=0.010)	1.01 (0.68-1.50, p=0.956)

Continuation of Table 4.21

Factors	Gradations	All of them	HR (single-factor)	HR (multivariate)
LDH	LDH is normal	205 (81.3)	–	–
	LDH is elevated	47 (18.7)	1.27 (0.90-1.80, p=0.172)	1.61 (1.04-2.49, p=0.031)
ESR	ESR's normal	124 (49.2)	–	–
	ESR's elevated	128 (50.8)	1.57 (1.19-2.06, p=0.001)	1.41 (0.97-2.06, p=0.072)
Platelets	platelets are normal	186 (73.8)	–	–
	platelets are elevated	22 (8.7)	1.48 (0.91-2.43, p=0.116)	1.17 (0.65-2.11, p=0.591)
	platelets are low	44 (17.5)	1.10 (0.76-1.58, p=0.625)	0.81 (0.52-1.24, p=0.328)
ECOG	ECOG0	19 (7.5)	–	–
	ECOG1	139 (55.2)	1.20 (0.71-2.04, p=0.487)	1.47 (0.81-2.64, p=0.201)
ECOG	ECOG2	79 (31.3)	1.54 (0.89-2.66, p=0.124)	1.51 (0.79-2.88, p=0.207)
	ECOG3	15 (6.0)	6.08 (2.91-12.69, p<0.001)	5.76 (2.19-15.12, p<0.001)
The drug in line 1	TKI	250 (99.2)	–	–
	IO	2 (0.8)	3.30 (0.46-23.87, p=0.238)	0.63 (0.07-5.92, p=0.683)
Metastasectomy	metastasectomy (-)	184 (73.0)	–	–
	metastasectomy (+)	68 (27.0)	0.67 (0.49-0.91, p=0.011)	0.58 (0.41-0.83, p=0.003)
Radiation therapy	radiation therapy (-)	210 (83.3)	–	–
	radiation therapy (+)	42 (16.7)	1.10 (0.77-1.57, p=0.593)	0.92 (0.60-1.41, p=0.709)

Table 4.21 shows that in the single-factor Cox analysis, the degree of tumor differentiation according to Fuhrman, bone and lung metastasis, elevation of ESR and

alkaline phosphatase, and metastasectomy were the factors influencing the OS in patients with single metastases of RCC. In Cox multivariate analysis, metastasis type, brain metastasis, LDH elevation, and metastasectomy were the factors influencing OS in patients with single metastases of RCC.

Thus, the study of survival rates in patients with single metastases of RCC in multivariate analysis showed the influence of the type of metastases, LDH level, and the presence of brain metastases.

4.2.3 Analysis of clinical and morphologic features metastatic lesions in patients with renal-cell carcinoma with multiple metastases

The study included 639 (65.1%) patients with multiple metastases of RCC. Clear-cell cancer was verified in 551 patients, papillary cancer in 31 patients, chromophobe cancer in 12 patients and other variants in 45 patients.

By grade of differentiation, G2 229 (35.8%) and G3 349 (54.6%) patients and patients with intermediate and poor prognosis 219 (34.3%) and 335 (52.4%) prevailed, respectively.

By categorizing the patients according to morphologic characteristics the following results were obtained.

Depending on the morphological characteristics of the tumor, the following results were obtained (Table 4.22).

Table 4.22 shows that patients with multiple RCC metastases were characterized by light-cell variants of RCC, more often G2 or G3. Other histologic variants with a low degree of differentiation were frequently encountered.

Table 4.22 – Distribution of patients with multiple metastases of RCC depending on the localization and histological characteristics of the tumor

Histologic variant	GRADE	Metastasis in bone, N	Metastasis into the lungs, N	Metastasis in the kidney	Metastasis to the adrenal gland	Metastasis into the liver	Metastasis to Lymph nodes	Metastasis into the brain	Other localizations of metastases
Clear-cell	1	19	51	7	9	11	32	4	21
	2	88	177	18	39	30	83	14	39
	3	115	22	21	35	60	142	16	58
Papillary	1	0	0	0	0	0	0	0	1
	2	6	12	1	3	2	1	2	0
	3	4	8	2	2	0	0	0	0
Chromophobic	1	0	0	0	0	0	0	0	0
	2	1	3	1	0	2	1	0	0
	3	2	4	2	0	1	3	0	0
Other	1	0	0	0	0	0	0	0	0
	2	1	2	0	0	1	2	1	0
	3	18	30	0	0	11	25	3	2

The presence of multiple metastases greatly complicated the analysis of this group due to the many (110) combinations of affected organs.

In patients with multiple metastases of clear cell RCC, at G1 (61 patients), lung and lymph node involvement was frequently observed (18.6%), followed by a combination of lung, lymph nodes and other localization (8.5%). In the third place by frequency of occurrence was the combined lesion of lungs and liver or lungs and other localizations (6.8% each).

In G2 (204 cases), patients with clear cell RCC often had isolated lung lesions (30 patients, 14.7%) or combined lung and bone lesions (26 patients, 12.7%), followed by lung+lymph nodes (18 patients, 8.8%) and lung+bone+lymph nodes (13 patients, 6.3%).

In G3 (286 cases), the same trend was observed in patients with clear cell RCC: isolated lung lesion and lung+lymph nodes were leading with a significant gap – 45 (15.7%) and 42 (14.6%) cases, respectively. The following combinations with approximately equal frequency of occurrence were next: bone lesions+metastases of other localizations – 19 cases (6.6%); bone lesions+lungs+lymph nodes and isolated multiple metastases in bones – 15 patients (5.2%) each.

Non-small cell variants of mRCC accounted for 88 cases (13.8%), and the same trend was observed with regard to the frequency of combinations as with small cell carcinomas: lung, bone, lymph nodes and combinations with other organs were dominant.

Comparison of the frequency of organ damage in patients with multiple metastases of RCC depending on the histological variant and degree of differentiation revealed statistically significant differences for all localizations (Table 4.23).

We found that bone lesions occurred in about half of all cases of clear cell cancer, while in non-small cell forms of RCC the frequency of bone lesions was about 1/3-1/4 of cases. The incidence of lung lesions in luminal cancer ranged from 77% to 86%, in non-small cell variants the percentage was lower – no more than 70% in G2 papillary cancer, on average – about 50%. Metastases to lymph nodes were detected in about half of patients with non-small cell variants of RCC (maximum in G1 – 55%). In patients with non-small cell variants of RCC, lymph nodes were affected less frequently, in about one third of cases, except for papillary cancer G3, in which changes reached up to 50%.

Table 4.23 – Frequency of metastatic organ involvement in patients with multiple metastases of RCC depending on histologic variant and degree of differentiation

Histologic variant of RCC	GRADE	There's no bone lesions	The bones are affected	There's no lung damage	The lungs are affected	Kidney's unaffected	Kidney's affected	Adrenal glands unaffected	The adrenal glands are affected	The liver's unaffected	The liver is affected	L\u's not affected.	They're affected.	Brain unaffected	The brain is affected	There are no other localizations	Other localizations are
Clear-cell	1	42 68.85 %	19 31.15 %	8 13.11 %	53 86.89 %	54 88.52 %	7 11.48 %	52 85.25 %	9 14.75 %	50 81.97 %	11 18.03 %	27 44.26 %	34 55.74 %	57 93.44 %	4 6.56 %	40 65.57 %	21 34.43 %
	2	116 56.86 %	88 43.14 %	27 13.24 %	177 86.76 %	186 91.18 %	18 8.82 %	165 80.88 %	39 19.12 %	174 85.29 %	30 14.71 %	144 50.35 %	83 40.69 %	190 93.14 %	14 6.86 %	165 80.88 %	39 19.12 %
	3	171 59.79 %	115 40.21 %	64 22.38 %	222 77.62 %	265 92.66 %	21 7.34 %	251 87.76 %	35 12.24 %	226 79.02 %	226 79.02 %	144 50.35 %	142 49.65 %	270 94.41 %	16 5.59 %	228 79.72 %	58 20.28 %
Papillary	2	11 64.71 %	66 35.29 %	5 29.41 %	12 70.59 %	16 94.12 %	1 5.88 %	14 82.35 %	3 17.65 %	15 88.24 %	2 11.76 %	11 64.71 %	6 35.29 %	15 88.24 %	2 11.76 %	12 70.59 %	5 29.41 %
	3	10 71.43 %	4 28.57 %	6 42.86 %	8 57.14 %	12 85.71 %	2 14.29 %	12 85.71 %	2 14.29 %	14 100.00 %	0 0.00 %	7 50 %	7 50 %	14 100.00 %	0	9 64.29 %	5 35.71 %

Continuation of Table 4.23

Histologic variant of RCC	GRADE	There's no bone lesions	The bones are affected	There's no lung damage	The lungs are affected	Kidney's unaffected	Kidney's affected	Adrenal glands unaffected	The adrenal glands are affected	The liver's unaffected	The liver's affected	L\u's not affected.	They're affected.	Brain unaffected	Brain is affected	There are no other localizations	Other localizations are
Chromophobic	2	4 80.00 % *p=.000451*	1 20.00 % *p=.000451*	2 40.00 % *p=.000002*	3 60.00 % *p=.000002*	4 80.00 % *p=.000026*	1 20.00 % *p=.000026*	5 100.00 % *p=.000363*	0 0.00 % *p=.000363*	3 60.00 % *p=.000064*	3 60.00 % *p=.000064*	4 80 % *p=.000024*	1 20 % *p=.000024*	5 100.00 % *p=.000753*	0 *p=.000753*	1 20.00 % *p=.000002*	4 80.00 % *p=.000002*
	3	5 71.43 % *p=.000451*	2 28.57 % *p=.000451*	3 42.86 % *p=.000002*	4 57.14 % *p=.000002*	5 71.43 % *p=.000026*	2 28.57 % *p=.000026*	6 85.71 % *p=.000363*	1 14.29 % *p=.000363*	6 85.71 % *p=.000064*	1 14.29 % *p=.000064*	4 57.14 % *p=.000024*	3 42.86 % *p=.000024*	7 100.00 % *p=.000753*	0 *p=.000753*	6 85.71 % *p=.000002*	1 14.29 % *p=.000002*
Other	2	2 66.67 % *p=.000451*	1 33.33 % *p=.000451*	1 33.33 % *p=.000002*	2 66.67 % *p=.000002*	3 100.00 % *p=.000026*	0 0.00 % *p=.000026*	3 100.00 % *p=.000363*	0 0.00 % *p=.000363*	2 66.67 % *p=.000064*	1 33.33 % *p=.000064*	1 33.33 % *p=.000024*	2 66.67 % *p=.000024*	2 66.67 % *p=.000753*	1 33.33 % *p=.000753*	2 66.67 % *p=.000002*	1 33.33 % *p=.000002*
	3	24 57.14 % *p=.000451*	18 42.86 % *p=.000451*	12 28.57 % *p=.000002*	30 71.43 % *p=.000002*	42 100.00 % *p=.000026*	0 0.00 % *p=.000026*	37 88.10 % *p=.000363*	5 11.90 % *p=.000363*	31 73.81 % *p=.000064*	11 26.19 % *p=.000064*	17 40.48 % *p=.000024*	25 59.52 % *p=.000024*	39 92.86 % *p=.000753*	3 7.14 % *p=.000753*	32 76.19 % *p=.000002*	10 23.81 % *p=.000002*
		χ^2*=43.1854, df=17, p=.000451*		χ^2*=59.0361, df=17, p=.000002*		χ^2*=51.3669, df=17, p=.000026*		χ^2*=43.8284, df=17, p=.000363*		χ^2*=48.8393, df=17, p=.000064*		χ^2*=51.5290, df=17, p=.000024*		χ^2*=41.6530, df=17, p=.000753*		χ^2*=58.6910, df=17, p=.000002*	

Metastases in the contralateral kidney also differed significantly depending on the histologic type: in luminal cell variant of RCC it was 7.3% in G2 and 11.48% in G3, while in non-small cell variant of RCC it exceeded 20%, reaching 28% in chromophobe cancer. Changes in the adrenal glands in multiple metastases of RCC were rare, without a clear trend by histologic variants, but a higher percentage of lesions in G2 of non-small cell cancer (19.2%) and papillary cancer (17.6%) was noteworthy. In multiple metastases of luminal RCC the liver was affected up to 20% of cases in G3, and in G3 chromophobe cancer the frequency of metastatic changes in the liver reached up to 40%, however, this subgroup is represented by only 5 cases. Metastases in the brain of RCC occurred in 5.5-7% depending on the histologic variant and degree of differentiation without a clear trend.

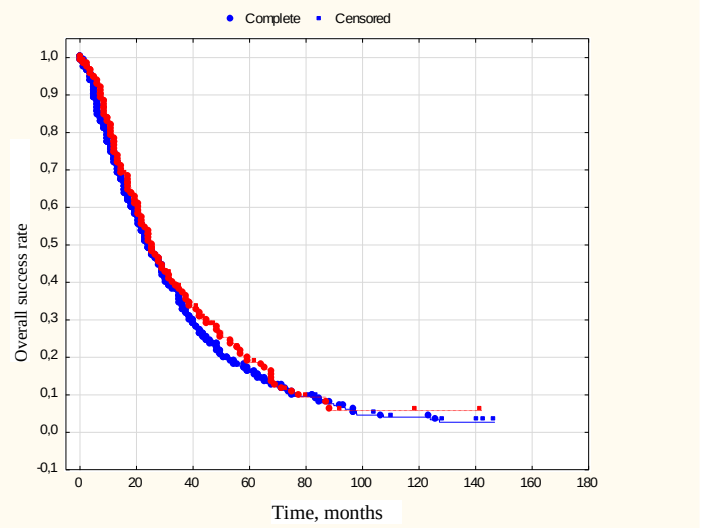
In evaluating the patients with multiple metastases of RCC included in the study, it was found that males predominated in 75.5% of cases in the study (Table 4.24).

Table 4.24 – Distribution of patients with multiple metastases of RCC depending on gender characteristics

Gender	Number of patients	HR
Men	476 (74.5)	–
Women	163 (25.5)	0.91 (0.75-1.12, p=0.379)

The OS rates in patients with multiple metastases of RCC according to gender (N=639) are shown in Figure 4.23.

Survival analysis showed that the rates of 3- and 5-year OS of patients with multiple metastases of RCC depending on sex were 38.5±1.4% and 17.2±1.3% in men, 39.5±1.4% and 19.6±1.6% in women, respectively (p=0.7). The median OS was 22 and 24 months, respectively.



p=0,7

Figure 4.23 – Kaplan-Meier curves of OS indicators in patients with multiple metastases of RCC depending on gender (N=639)

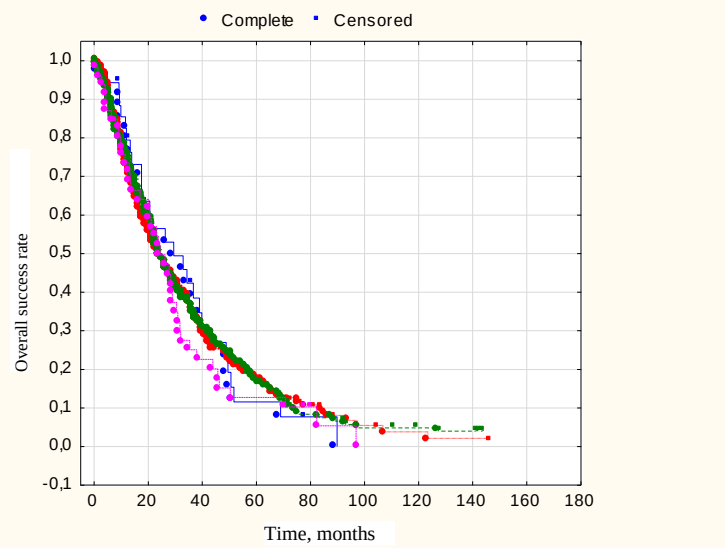
Thus, in the present study, there was no advantage in OS and median OS rates according to gender in patients with multiple metastases of RCC (p=0.7).

In evaluating the patients with multiple metastases of RCC included in the study, it was found that the study was dominated by patients in the age range of 60-74 years at 47.7% (Table 4.25).

Table 4.25 – Distribution of patients with multiple metastases of RCC depending on age

Age	Number of patients	HR
18-44	35 (5.5)	–
45-59	254 (39.7)	1.00 (0.67-1.48, p=0.984)
60-74	305 (47.7)	0.98 (0.66-1.45, p=0.919)
over 75	45 (7.0)	1.14 (0.70-1.85, p=0.596)

The rates of OS in patients with multiple metastases of RCC depending on age are presented in Figure 4.24.



p=0,85

Figure 4.24 – Kaplan-Meier curves of OS indicators in patients with multiple metastases of RCC depending on age (N=639)

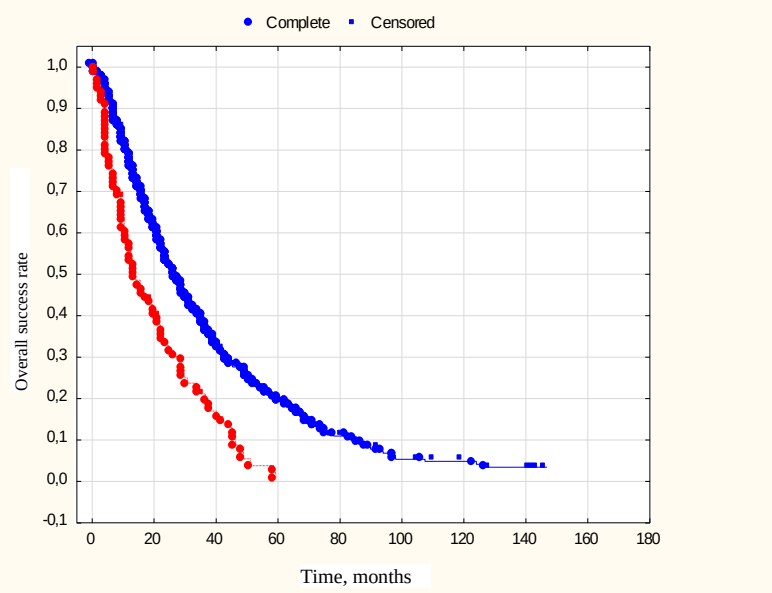
Figure 4.24 shows that the 3- and 5-year OS rates of patients with multiple metastases of RCC according to age were 43.7±1.5% and 10.6±1.2%, 40.6±1.5% and 17.5±1.3%, 38.5±1.4% and 18.2±1.3%, 23.7±1.3% and 9.8±1.2%, respectively. The median OS was 28, 29, 29 and 28 months, respectively. Thus, there is no advantage in OS and median OS according to age in patients with multiple metastases of RCC (p=0.85).

In the evaluation of patients with multiple metastases of RCC included in the study, it was found that the study was dominated by patients with the presence of SCR in 86.2% (Table 4.26).

Table 4.26 – Distribution of patients with multiple metastases of RCC depending on the histological variant of the tumor

Histologic variant	Number of patients	HR
Clear-cell	551 (86.2)	–
Non-small cell cancer	88 (13.8)	1.98 (1.56-2.52, p<0.001)

The OS rates in patients with multiple metastases of RCC depending on the histological variant of the tumor are presented in Figure 4.25.



p<0,0001

Figure 4.25 – Kaplan-Meier curves of OS indicators in patients with multiple metastases of RCC depending on the histological variant of the tumor (N=639)

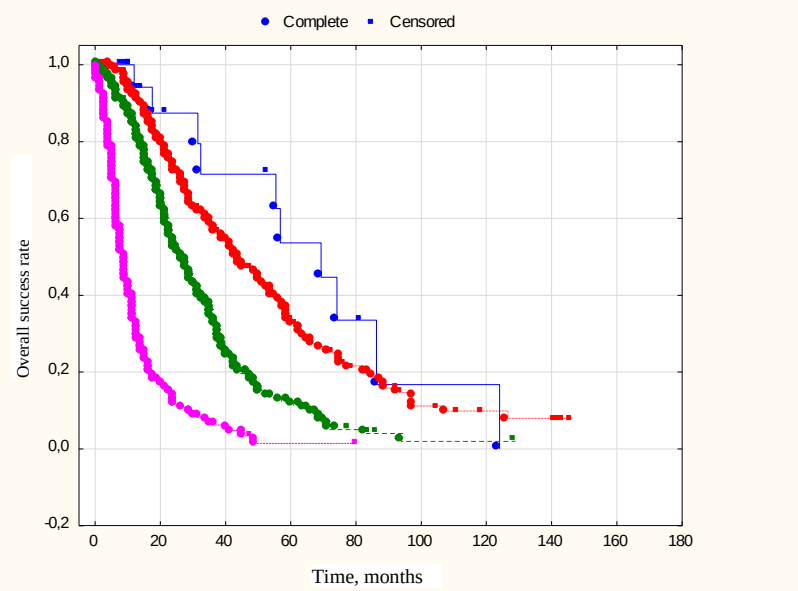
Figure 4.25 shows that the 3- and 5-year OS rates of patients with multiple metastases with luminal and non-small cell mRCC were 39.2±1.4% and 20.2±1.3%, 20.4±1.3% and 2.3±1.1%, respectively. The median OS also differed and was 26 and 16 months, respectively. Thus, the conducted study showed significant differences in OS and median OS depending on the histological subtype of tumor in patients with multiple metastases of RCC (p<0.0001).

When evaluating the patients with multiple metastases of RCC included in the study according to ECOG status, Table 4.27 shows that patients with ECOG 2-3 predominated in 63% of cases.

Table 4.27 – Distribution of patients with multiple metastases of mRCC depending on ECOG status

ECOG Status	Number of patients	HR
ECOG0	24 (3.8)	–
ECOG1	212 (33.2)	1.48 (0.78-2.80, p=0.235)
ECOG2	246 (38.5)	2.90 (1.53-5.48, p=0.001)
ECOG3	157 (24.6)	9.58 (5.02-18.31, p<0.001)

The OS rates in patients with multiple metastases of RCC depending on ECOG status are presented in Figure 4.26.



p<0,0001

Figure 4.26 – Kaplan-Meier curves of OS indicators in patients with multiple metastases of RCC depending on ECOG status (N=639)

As we can see from Figure 4.26, the rates of OS depend on ECOG status and the rates of 3- and 5-year OS of RCC patients were 72.8±1.8% and 53.6±1.6%, 58.2±1.6% and 37.1±1.4%, 38.4±1.4% and 13.3±1.3%, 6.2±1.2% and 1.3±1.1%, respectively. The median OS at ECOG 0,1,2,3 also differed and was 67, 41, 25 and 9 months, respectively. Thus, the study revealed statistically significant differences in

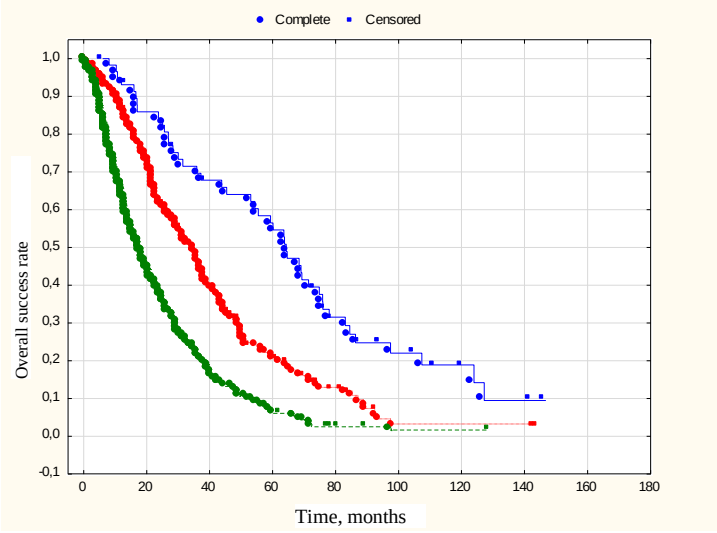
OS and median OS in patients with multiple metastases of RCC depending on ECOG status (p<0.0001).

When evaluating patients with multiple metastases of RCC included in the study according to the degree of tumor differentiation, the patients were divided into 3 groups. Table 4.28 shows that G1 was detected in 59 (9.2%), G2 and G3 in 229 (35.8%) and 351 (54.9%) patients, respectively. Thus, our study was dominated by patients with low-differentiated tumor in 55% of cases.

Table 4.28 – Distribution of patients with single metastases of mRCC depending on the degree of tumor differentiation according to Fuhrman

Degree of differentiation	Number of patients	HR
Grade 1	59 (9,2)	–
Grade 2	229 (35,8)	1,93 (1,38-2,70, p<0,001)
Grade 3	351 (54,9)	3,74 (2,69-5,20, p<0,001)

The OB rates in patients with multiple metastases of RCC depending on the degree of tumor differentiation are presented in Figure 4.27.



p<0,0001

Figure 4.27 – Kaplan-Meier curves of OS indicators in patients with multiple metastases of RCC depending on the degree of tumor differentiation according to Fuhrman (N=639)

As shown in Figure 4.27, the OS rates are directly related to the degree of tumor differentiation according to Fuhrman and the 3- and 5-year OS rates of patients were 68.9±1.7% and 53.3±1.5%, 46.4±1.5% and 20.5±1.3%, 22.1±1.3% and 6.4±1.1%, respectively. The median OS also differed at G1, G2, and G3 and was 63, 32, and 17 months, respectively. Thus, the conducted study revealed statistically significant differences in OS and median OS depending on the degree of tumor differentiation according to Fuhrman in patients with multiple metastases of RCC ($p<0.0001$).

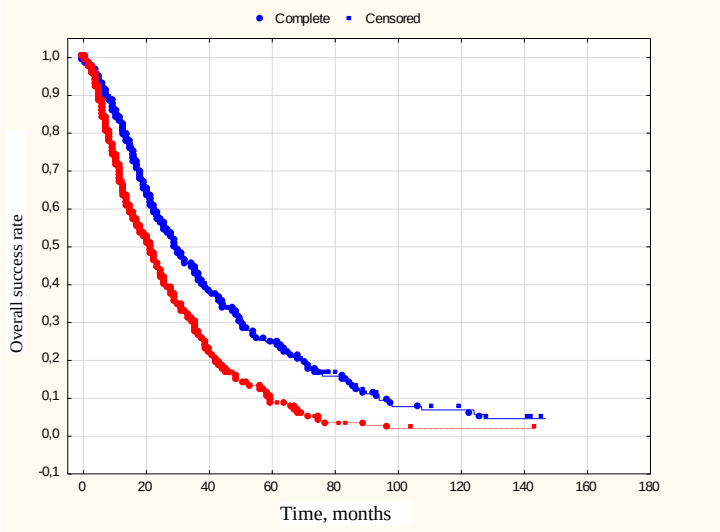
When evaluating patients with multiple metastases of RCC included in the study according to the type of metastases, patients with metachronous and synchronous metastases were equally distributed around 50% (Table 4.29).

Table 4.29 – Distribution of patients with multiple metastases of mRCC depending on the type of metastases

Type of metastasis	Number of patients	HR
Synchronous	314 (49.1)	–
Metachronous	325 (50.9)	0.62 (0.52-0.73, $p<0.001$)

The rates of OS in patients with multiple metastases of RCC depending on the time of metastases appearance are presented in Figure 4.28.

Figure 4.28 shows that the 3- and 5-year OS rates of patients with multiple metachronous and synchronous metastases of RCC were 44.9±1.5% and 24.4±1.3%, 29.7±1.3% and 8.8±1.2%, respectively. The median OS was 28 and 22 months, respectively. Thus, statistically significant differences in OS and median OS were found in patients with multiple synchronous and metachronous metastases of RCC ($p<0.0001$).



p<0,0001

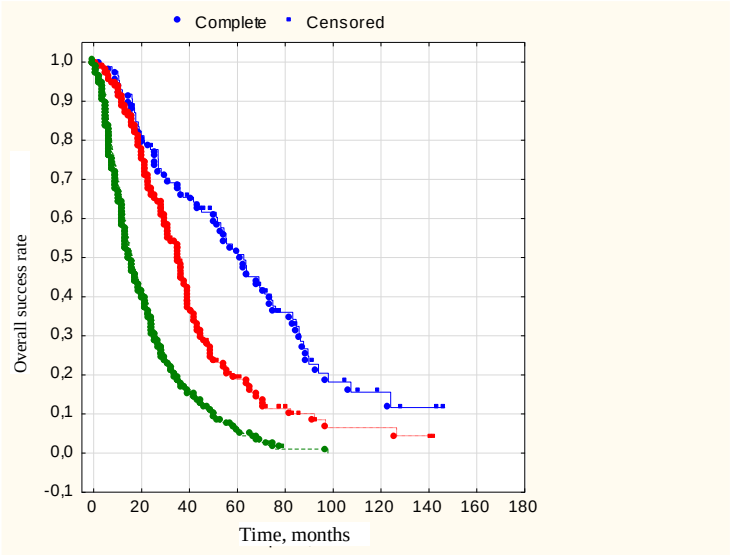
Figure 4.28 – Kaplan-Meier curves of patients OS indicators with multiple metachronous and synchronous metastases of RCC (N=639)

Although we consider separately the factors included in the IMDC prognostic model, we also evaluated survival rates in 3 prognostic groups in the overall cohort of patients with multiple RCC metastases. When evaluating the patients with multiple metastases of RCC included in the study according to the number of prognostic factors according to the IMDC classification, the patients were categorized into 3 groups. Table 4.30 shows that the number of patients with favorable prognosis was 85 (13.3%), intermediate and poor prognosis 219 (34.3%) and 335 (52.4%) patients, respectively. Thus, it is important to note that more than half of the patients with multiple metastases of mRCC were in the IMDS poor prognosis group.

Table 4.30 – Distribution of patients with multiple metastases of RCC depending on IMDC prognosis

IMDC Forecast	Number of patients	HR
Favorable	85 (13.3)	–
Intermediate	219 (34.3)	1.87 (1.38-2.53, p<0.001)
Poor	335 (52.4)	4.30 (3.22-5.75, p<0.001)

The OS rates in patients with multiple metastases of RCC depending on IMDC prognosis are presented in Figure 4.29.



p<0,0001

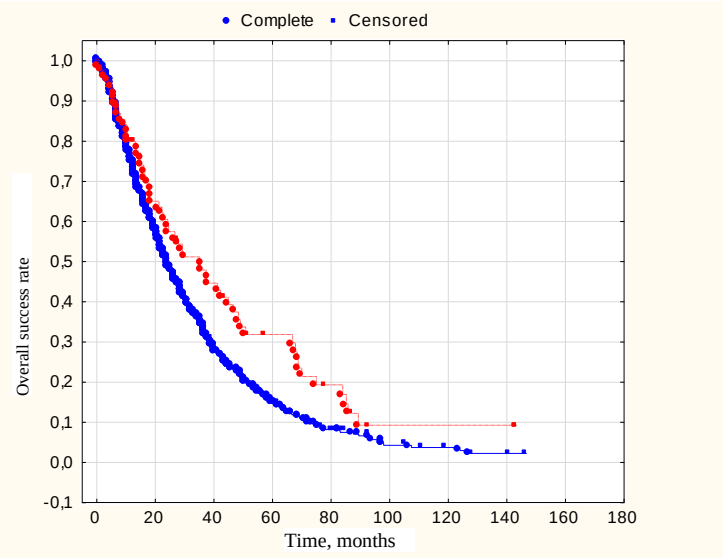
Figure 4.29 – Kaplan-Meier curves of OS indicators in patients with multiple metastases depending on IMDC prognosis (N=639)

As can be seen from Figure 4.29, the survival rates directly depend on the prognosis according to the IMDC scale. Thus, in the group of mRCC patients with a favorable prognosis, the 3-year and 5-year survival rates were 66.8±1.7% and 50.6±1.5%, and in the group with an intermediate prognosis – 54.2±1.6% and 19.7±1.3%, respectively. And the OS rates in the poor prognosis group were 19.3±1.3% and 1.3±1.1%. And the median OS in IMDC prognosis groups also differed and were 61, 37 and 17 months, respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on IMDC prognosis in patients with multiple metastases of RCC (p<0.0001).

Radiation therapy in patients with multiple metastases of mRCC is summarized in Table 4.31 and Figure 4.30.

Table 4.31 – Distribution of patients with multiple metastases of RCC depending on the provision/absence of radiation therapy

Radiation therapy	Number of patients	HR
Radiation therapy (-)	565 (88.4)	–
Radiation therapy (+)	74 (11.6)	0.71 (0.53-0.94, p=0.015)



p=0,001

Figure 4.30 – Kaplan-Meier curves of patients OS indicators
with multiple metastases of RCC
in the presence/absence of radiation therapy (N=639)

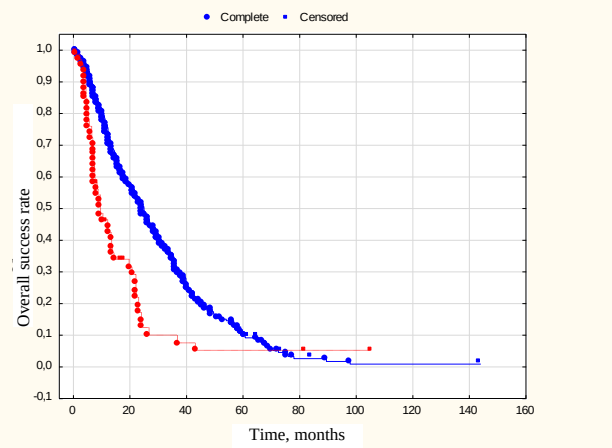
As shown in Figure 4.30, the 3- and 5-year OS of patients with multiple metastases of RCC with and without radiation therapy were 49.8±1.5% and 30.7±1.4%, 32.7±1.4% and 16.1±1.3%, respectively. The median OS was 27 and 22 months, respectively. Thus, there was an advantage in the rates of OS during radiotherapy in patients with multiple metastases of RCC (p=0,001).

In evaluating patients with multiple metastases of RCC included in the study, it was found that CN was performed in 569 (89.0%) patients (Table 4.32).

Table 4.32 – Distribution of patients with sporadic metastases of mRCC depending on the presence/absence of CN

NE	Number of patients	HR
CN (+)	569 (89.0)	–
CN (-).	70 (11.0)	2.50 (1.89-3.32, p<0.001)

CN in patients with multiple metastases of mRCC is presented in Figure 4.31.



p<0,0001

Figure 4.31 – Kaplan-Meier curves of OS indicators
in patients with multiple metastases of RCC
depending on the presence/absence of CN (N=639)

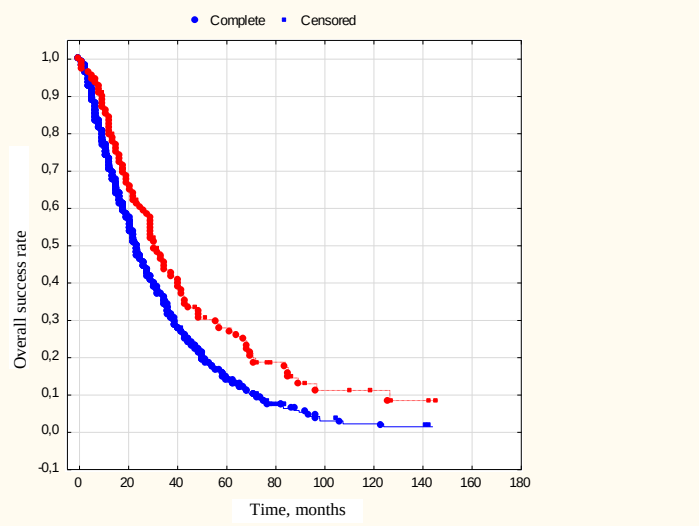
Survival analysis showed that the 3- and 5-year OS rates of patients with multiple metastases of RCC with and without CN were 35.4±1.4% and 9.8±1.2%, 9.9±1.2% and 5.2±1.2%, respectively. Meanwhile, the median OS was also higher in RCC patients when CN was performed and was 24 and 10 months, respectively. Thus, the study showed differences in OS and median OS depending on the performance of CN in patients with multiple metastases of RCC (p<0.0001).

In the evaluation of patients with multiple metastases of RCC included in the study, it was found that metastasectomy was performed in 123 (19.2%) patients (Table 4.33).

Table 4.33 – Distribution of patients with multiple metastases of mRCC depending on the performance/absence of metastasectomy

Metastasectomy	Number of patients	HR
Metastasectomy (-)	516 (80.8)	–
Metastasectomy (+)	123 (19.2)	0.68 (0.54-0.85, p=0.001)

Metastasectomy in patients with multiple metastases of mRCC is presented in Figure 4.32.



p=0,0007

Figure 4.32 – Kaplan-Meier curves of OS indicators in patients with multiple metastases of RCC depending on the presence/absence of metastasectomy (N=639)

The presented Kaplan-Meier curves demonstrated that the 3- and 5-year OS rates of patients with multiple RCC metastases with and without metastasectomy were 43.4±1.4% and 28.9±1.3%, 35.1±1.4% and 14.8±1.3%, respectively. Meanwhile, the median OS was also higher in RCC patients when metastasectomy was performed and was 31 and 23 months, respectively. Thus, the study showed differences in OS and median OS depending on metastasectomy in patients with multiple metastases of RCC (p=0.0007).

Thus, the histological variant and degree of tumor differentiation according to Fuhrman, the type of metastases, performance of CN and metastasectomy, as well as

radiation therapy were the factors influencing the OS in patients with multiple metastases of RCC.

A single- and multivariate analysis was performed to analyze the influence of prognostic factors on OS in patients with multiple metastases of RCC (Table 4.34).

Table 4.34 – Cox proportional hazards model of the effect on OS rates in the group of patients with multiple metastases of RCC (N=639)

Factors	Gradations	Sick people (%)	HR (single-factor)	HR (multivariate)
Gender	men	475 (74.5)	–	–
	women	163 (25.5)	0.91 (0.75-1.11, p=0.352)	0.89 (0.72-1.09, p=0.264)
Age	18-44	35 (5.5)	–	–
	45-59	253 (39.7)	1.00 (0.68-1.49, p=0.981)	1.22 (0.80-1.85, p=0.353)
	60-74	305 (47.8)	0.98 (0.66-1.45, p=0.919)	1.10 (0.73-1.67, p=0.637)
	over 75	45 (7.1)	1.14 (0.70-1.85, p=0.596)	1.04 (0.62-1.74, p=0.880)
Localization	on the right	320 (50.2)	–	–
	on the left	301 (47.2)	0.96 (0.81-1.15, p=0.673)	0.97 (0.81-1.17, p=0.758)
	bilateral	17 (2.7)	1.04 (0.60-1.82, p=0.888)	0.78 (0.43-1.41, p=0.411)
CN	CN (+)	568 (89.0)	–	–
	CN (-)	70 (11.0)	2.49 (1.88-3.31, p<0.001)	2.01 (1.46-2.76, p<0.001)
Histological variant	clear-cell	550 (86.2)	–	–
	non- clear-cell	88 (13.8)	1.97 (1.55-2.51, p<0.001)	1.39 (1.07-1.81, p=0.015)

Continuation of Table 4.34

Factors	Gradations	Sick people (%)	HR (single-factor)	HR (multivariate)
Degree of differentiation	1	59 (9.2)	–	–
	2	228 (35.7)	1.95 (1.39-2.73, p<0.001)	1.67 (1.15-2.42, p=0.007)
	3	351 (55.0)	3.75 (2.69-5.21, p<0.001)	1.87 (1.27-2.74, p=0.001)
Type of metastasis	synchronous	314 (49.2)	–	–
	metachronous	324 (50.8)	0.62 (0.52-0.74, p<0.001)	1.31 (1.05-1.64, p=0.017)
Bones	bone mts (-)	385 (60.3)	–	–
	bone mts (+)	253 (39.7)	1.21 (1.02-1.45, p=0.032)	1.02 (0.81-1.29, p=0.856)
Lungs	mts to the lungs (-)	127 (19.9)	–	–
	mts to the lungs (+)	511 (80.1)	0.80 (0.65-0.99, p=0.037)	0.82 (0.65-1.04, p=0.097)
Liver	mts to the liver (-)	520 (81.5)	–	–
	mts to the liver (+)	118 (18.5)	1.25 (1.01-1.56, p=0.044)	0.97 (0.72-1.30, p=0.816)
Brain	brain mts (-)	598 (93.7)	–	–
	brain mts (+)	40 (6.3)	1.08 (0.74-1.58, p=0.691)	1.58 (1.04-2.40, p=0.031)
Hemoglobin	hemoglobin is normal	393 (61.6)	–	–
	anemia	245 (38.4)	2.69 (2.25-3.21, p<0.001)	1.98 (1.59-2.46, p<0.001)
Alkaline phosphatase	alkaline phosphorus is normal	382 (59.9)	–	–
	alkaline phosphorus is elevated	256 (40.1)	1.44 (1.21-1.72, p<0.001)	0.91 (0.72-1.15, p=0.412)

Continuation of Table 4.34

Factors	Gradations	Sick people (%)	HR (single-factor)	HR (multivariate)
LDH	LDH is normal	448 (70.2)	–	–
	LDH is elevated	190 (29.8)	1.24 (1.03-1.49, p=0.023)	1.07 (0.84-1.35, p=0.587)
ESR	ESR's normal	200 (31.3)	–	–
	ESR's elevated	438 (68.7)	1.58 (1.31-1.91, p<0.001)	1.02 (0.81-1.28, p=0.856)
Platelets	platelets are normal	423 (66.3)	–	–
	thrombocytosis	118 (18.5)	1.77 (1.42-2.21, p<0.001)	1.29 (0.97-1.70, p=0.076)
	thrombocytopenia	97 (15.2)	1.46 (1.15-1.86, p=0.002)	1.16 (0.87-1.53, p=0.306)
ECOG	ECOG0	24 (3.8)	–	–
	ECOG1	212 (33.2)	1.48 (0.78-2.81, p=0.235)	1.44 (0.73-2.85, p=0.294)
ECOG	ECOG2	245 (38,4)	2.93 (1.55-5.54, p=0.001)	2.39 (1.20-4.74, p=0.013)
	ECOG3	157 (24,6)	9.61 (5.03-18.37, p<0.001)	4.88 (2.37-10.02, p<0.001)
A drug in 1 line	TKI	607 (95,1)	–	–
	IO	31 (4,9)	0.36 (0.11-1.12, p=0.076)	0.69 (0.22-2.17, p=0.523)
Metastasectomy	metastasectomy (-)	515 (80,7)	–	–
	metastasectomy (+)	123 (19,3)	0.67 (0.54-0.85, p=0.001)	0.71 (0.55-0.92, p=0.009)
Radiation therapy	radiation therapy (-)	564 (88,4)	–	–
	radiation therapy (+)	74 (11,6)	0.70 (0.53-0.93, p=0.014)	0.73 (0.53-1.01, p=0.061)

Table 4.34 shows that in the single-factor Cox analysis, tumor histologic variant, Fuhrman tumor differentiation grade, metastasis type, bone, lung, and liver metastases; elevated alkaline phosphatase, LDH, and ESR; and performance of CN, metastasectomy, and radiation therapy were the factors influencing the OS in patients with multiple metastases of RCC. In multivariate analysis according to Cox, tumor histological variant, tumor differentiation degree according to Fuhrman, type of metastases, brain metastases, as well as performance of CN, metastasectomy were the factors influencing the OS in patients with multiple metastases of RCC.

The study of survival rates in patients with multiple metastases of RCC in multivariate analysis showed the influence of the histological variant of the tumor, the degree of tumor differentiation according to Fuhrman and the type of metastases, the performance of CN and metastasectomy, as well as the presence of metastases to the brain.

Thus, despite the existing tendency of lung, bone and lymph node involvement by RCC metastases, histologic variants and the degree of RCC differentiation imposed their imprint on the features of the metastatic process, which should be taken into account when choosing the tactics of further treatment, which will improve the survival rate and quality of life.

4.3 Dependence of survival rates in patients with synchronized and metachronous metastases of renal cell carcinoma

Synchronous metastases were detected in 403 (41.1%) mRCC patients, metachronous metastases in 578 (58.9%) patients. And in the work of F. Donskov et al. synchronous metastases were found in about 15% of patients with mRCC [230, 246].

The distribution by number of organs affected was as follows (Table 4.35).

Table 4.35 – Number of metastatic organs in patients with synchronous and metachronous metastases of RCC

Number of organs with metastases	Synchronous	Metachronous	χ^2 ; p-value
Lesion of 1 organ	15 (3.7%)	67 (11.6%)	χ^2=19.2; p=0.000
2 organ damage	114 (28.2%)	244 (42.2%)	χ^2=19.8; p=0.000
Lesion of 3 or more organs	274 (67.9%)	267 (46.2%)	χ^2=49.9; p=0.000

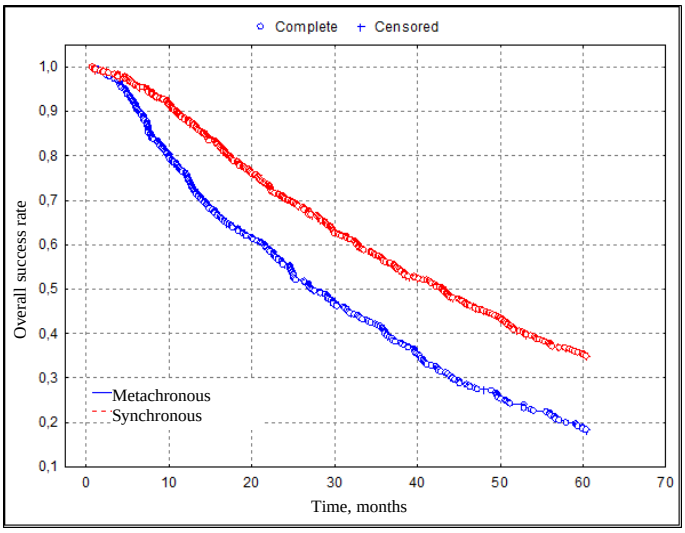
Table 4.35 shows that the lesion of 1 and 2 organs was more often observed in patients with metachronous metastases of RCC, and in synchronous metastases the lesion of 3 organs and more was more often established, because after removal of the primary tumor the patient was under constant dynamic observation of doctors, which allowed detecting metastatic lesions in a timely manner.

Table 4.36 shows that synchronous metastases of RCC were more frequently observed in bone, while no differences were found in other localizations.

Table 4.36 – Frequency of metastasis localization in patients with synchronous and metachronous metastases of RCC

Localization of mts	Synchronous	Metachronous	χ^2 ; p-value
Lungs	273 (67.7)	382 (66.1)	p>0.05
Bones	181 (44.9)	169 (29.2)	p<0.001
Lymph nodes	157 (38.9)	176 (30.4)	p>0.05
Liver	66 (16.4)	75 (13.0)	p>0.05
Adrenal gland	55 (13.6)	67 (11.6)	p>0.05
Kidney	28 (6.9)	45 (7.8)	p>0.05
Brain	29 (7.2)	27 (4.7)	p>0.05

The OS indicators are presented in Figure 4.33.



p=0,0001

Figure 4.33 – Kaplan-Meier curves of OS indices of mRCC patients (N=981) with synchronous and metachronous metastases

The presented Kaplan-Meier curves demonstrated that the 3- and 5-year OS rates of patients with metachronous and synchronous metastases of RCC patients were 53.7±1.7% and 35.1±1.6%, 38.2±1.8% and 18.5±1.4%, respectively, respectively. Meanwhile, the median OS was also higher in patients with synchronous metastases of RCC were 43 and 27 months, respectively. Thus, the study showed differences in OS and median OS depending on the time of metastases occurrence in RCC patients (p=0.0001).

Based on the differences identified, we searched for factors with potential impact on prognosis in patients with synchronous and metachronous metastases of RCC (Table 4.37).

Table 4.37 shows that patients with synchronous metastases of RCC more often had poor prognosis according to IMDC and ECOG status, low degree of tumor differentiation, histologically – non-small cell carcinoma variants, presence of lymphogenic metastases and a greater number of organs affected by hematogenous metastases, i.e. from the point of view of prognostic factors generally accepted in oncology had a poorer status.

Table 4.37 – Comparison of baseline characteristics of patients with synchronous (N=403) and metachronous (N=578) mRCC

Signs	Synchronous metastases	Metachronous metastases	χ^2 ; p-value
Men Women	294 (72.9) 109 (27.1)	410 (70.9) 168 (29.1)	χ^2=0.59; p=0.44
Age, years (M±SD; Me (Q_{25} -Q_{75})))	59.4±9.6 60 (53-65)	61.7±9.8 62 (55-69)	p>0.05
Prior radical surgery Yes No	 330 (81.9) 73 (18.1)	 571 (98.8) 7 (1.2)	 χ^2=79.5; p<0.001
ECOG status 0 -1 2-3	 130 (32.2) 273 (67.7)	 326 (56.4) 252 (43.6)	 χ^2=64.4; p<0.001
IMDC Criteria Favorable outlook Intermediate Poor	 23 (5.7) 103 (25.6) 277 (68.7)	 203 (35.1) 249 (43.1) 126 (21.8)	 χ^2=238; p<0.001
T1-T2 T3- T4	97 (24.1) 306 (75.9)	257 (44.5) 321 (55.5)	χ^2=38.3; p<0.001
No N1	255 (63.3) 148 (36.7)	505 (87.4) 73 (12.6)	χ^2=67.6; p<0.001
Tumor differentiation according to Fuhrman G_1 -G_2 G_3	 143 (35.5) 260 (64.5)	 403 (69.7) 175 (30.3)	 χ^2=121; p<0.001
Histopathologic type Clear-cell Non-small cell	 338 (83.9) 65 (16.1)	 529 (91.5) 49 (8.5)	 χ^2=12.8; p<0.001

Table 4.38 shows that lower than normal hemoglobin levels and elevated ESR were more frequently observed in patients with synchronous metastases while patients with metachronous metastases were more likely to have normal platelet counts and alkaline phosphate counts.

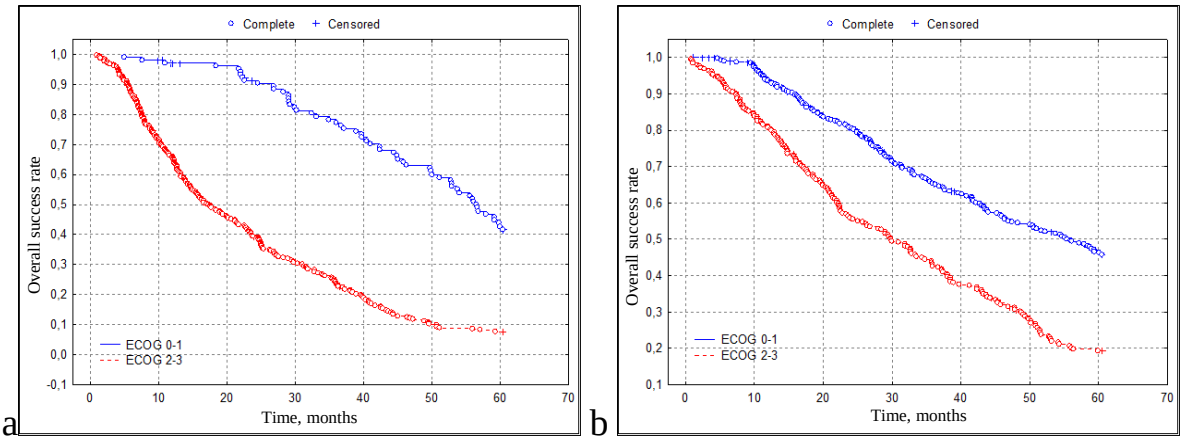
Table 4.38 – Comparison of laboratory parameters in patients with synchronous and metachronous mRCC

Signs	Norma	Synchronous metastases	Metachronous metastases	χ^2 ; p-value
Hemoglobin	norm Hb <NGH	245 (60.1) 158 (39.9)	428 (74) 150 (26)	χ^2=21.6; p<0.001
Neutrophils	norm Neu<NGN Neu> ULN	301 (74.7) 60 (14.9) 42 (10.4)	454 (78.5) 57 (9.9) 67 (11.6)	χ^2=2.6; p=0.28
LDH	norm LDH>ULN	285 (70.7) 118 (29.3)	437 (75.6) 141 (24.4)	χ^2=3.0; p=0.08
Platelets	norm >ULN <NGN	251 (62.2) 76 (18.9) 76 (18.9)	428 (74.1) 74 (12.8) 76 (13.1)	χ^2=16.6; p<0.001
Alkaline phosphatase	norm CF>ULN	244 (60.5) 159 (39.5)	393 (68) 185 (32)	χ^2=4.7; p=0.02
Calcium level	norm Ca>ULN unknown	123 (30.5) 64 (15.9) 216 (-)	187 (32.3) 98 (16.9) 293 (-)	χ^2=0.005; p=0.98
ESR	norm >ULN	118 (29.3) 285 (70.7)	255 (45.3) 323 (54.7)	χ^2=24.6; p<0.001

Thus, lesions of 1 and 2 organs were more frequently observed in patients with metachronous metastases of RCC. Bone metastases were more frequent in synchronous metastases. Patients with synchronous metastases of RCC more often had poor prognosis according to IMDC and ECOG status, higher T category, low degree of tumor differentiation, histologically – non-small cell carcinoma variants, presence of lymphogenic metastases and a greater number of affected organs.

4.3.1 Study of the influence of clinical and laboratory factors on overall patient survival rates with synchronous and metachronous metastases renal cell carcinoma

As can be seen in Figure 4.34, the survival rates directly depend on the general condition of patients with synchronous and metachronous metastases of RCC. Thus, the 3-year and 5-year OS of patients with synchronous and metachronous metastases at ECOG 0-1 status were 77.5±1.6% and 42.9±1.4%, 63.6±1.7% and 46.9±1.6%, respectively. The median OS was 56 and 55 months, respectively. And for ECOG 2-3 status, the 3-year and 5-year OS rates of patients with synchronous and metachronous metastases were 21.8±1.4% and 40.8±1.6%, 9.1±1.3% and 9.8±1.3%, respectively. The median OS was 17 and 30 months, respectively.

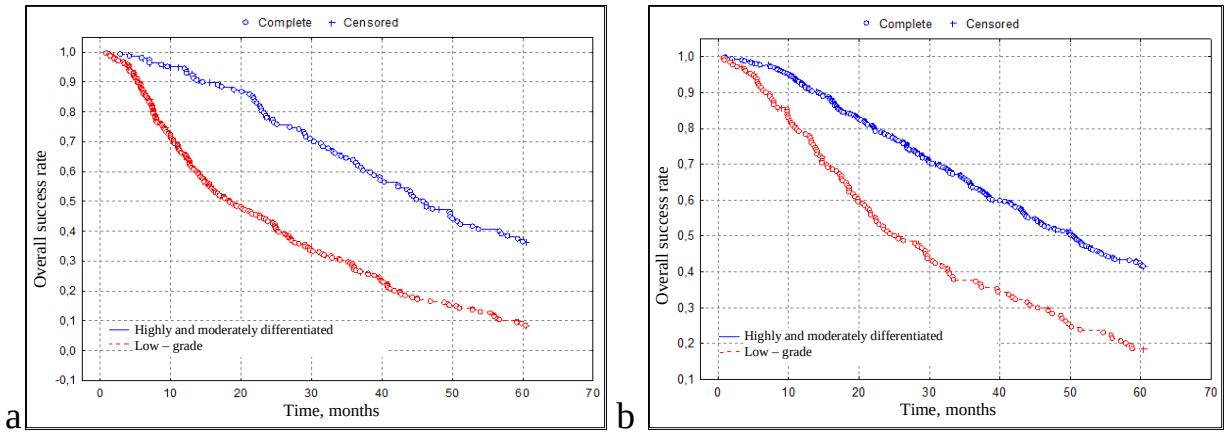


p<0,0001

Figure 4.34 – Comparison of Kaplan-Meier curves of OS indicators RCC patients with synchronous (a) and metachronous (b) metastases at ECOG 0-1 and ECOG 2-3

Thus, ECOG status had a statistically significant effect on the OS and median OS in the group of patients with synchronous RCC metastases and those with metachronous metastases, with survival rates of patients with synchronous RCC metastases being significantly worse (p<0.0001).

As can be seen in Figure 4.35, the OS rates directly depend on the tumor differentiation according to Fuhrman and the presented diagram of Kaplan-Meier curves shows, that 3-year and 5-year OS of patients with synchronous and metachronous metastases of RCC in highly and moderately differentiated tumors were 60.1±1.7%, 36.5±1.5%, 62.2±1.9% and 41.8±1.6%, respectively, in low-differentiated tumors – 27.7±1.5%, 8.9±1.3%, 37.5±1.8% and 18.4±1.4%, respectively. The median OS was 45 and 50 months in G1-2 and 18 and 25 months in G3, respectively.



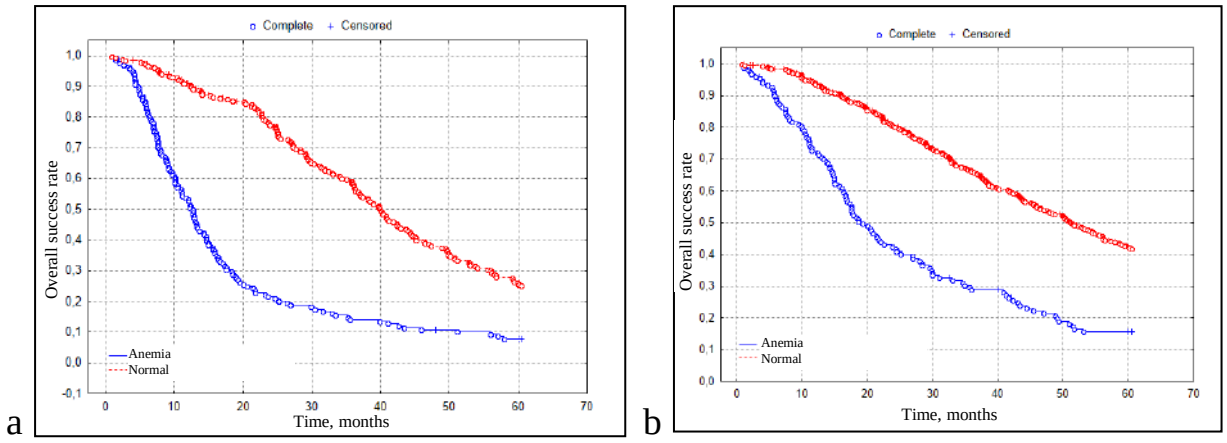
p<0,0001

Figure 4.35 – Comparison of Kaplan-Meier curves of patients OS indicators with synchronous (a) and metachronous (b) metastases of RCC at G1-2 and G3

Thus, the study showed that the degree of tumor differentiation had a statistically significant effect on the OS and median OS in patients with synchronous and metachronous metastases of RCC (p<0.0001).

The presented diagram (Figure 4.36) of Kaplan-Meier curves shows that the 3-year and 5-year OS of patients with synchronous and metachronous metastases with hemoglobin in normal hemoglobin (135-160 and 120-140 g/L) were 53.8±1.6% and 25.5±1.4%, 64.7±1.5% and 41.9±1.6%, respectively. The median OS at hemoglobin normal in patients with synchronous and metachronous metastases was 40 and 51 months, respectively. And the 3-year and 5-year OS rates of patients with anemia

(below 120-135 g/L) were 13.5±1.4% and 7.8±1.3%, 28.6±1.5% and 15.6±1.4% for synchronous and metachronous metastases, respectively.

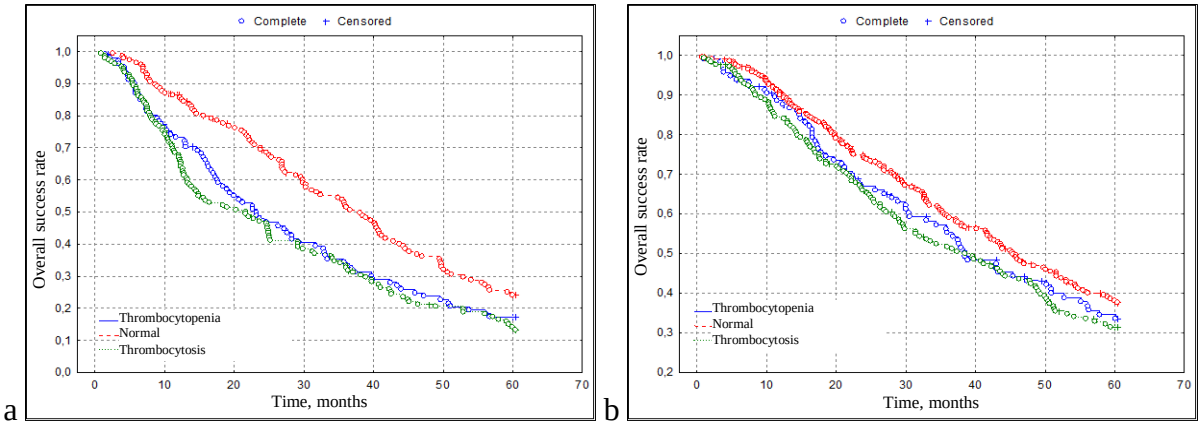


p<0,0001

Figure 4.36 – Comparison of OS indicators of patients with synchronous (a) and metachronous (b) metastases of RCC depending on hemoglobin level, with hemoglobin norm 135-160 g/L in men and 120-140 g/L in women

The median OS was 12 and 19 months, respectively. Thus, the hemoglobin level had a significant effect on OS and median OS for both patients with synchronous and metachronous metastases of RCC (p<0.0001).

The presented diagram (Figure 4.37) of the Kaplan-Meier curves shows that the 3-year and 5-year OS rates for platelet normal (150-400 U/μL) in patients with synchronous and metachronous metastases were 50.1±1.6% and 23.3±1.3%, 58.4±1.5% and 27.5±1.4%, respectively. Meanwhile, the median OS for patients with synchronous and metachronous metastases of RCC was 37 and 45 months, respectively. And the rates of 3-year and 5-year overall OS for thrombocytosis (above 400 U/μL) in patients with synchronous and metachronous metastases of RCC were 30.6±1.5% and 10.4±1.3%, 49.9±1.5% and 28.8±1.4%, respectively. Median OS was 20 and 38 months, respectively.

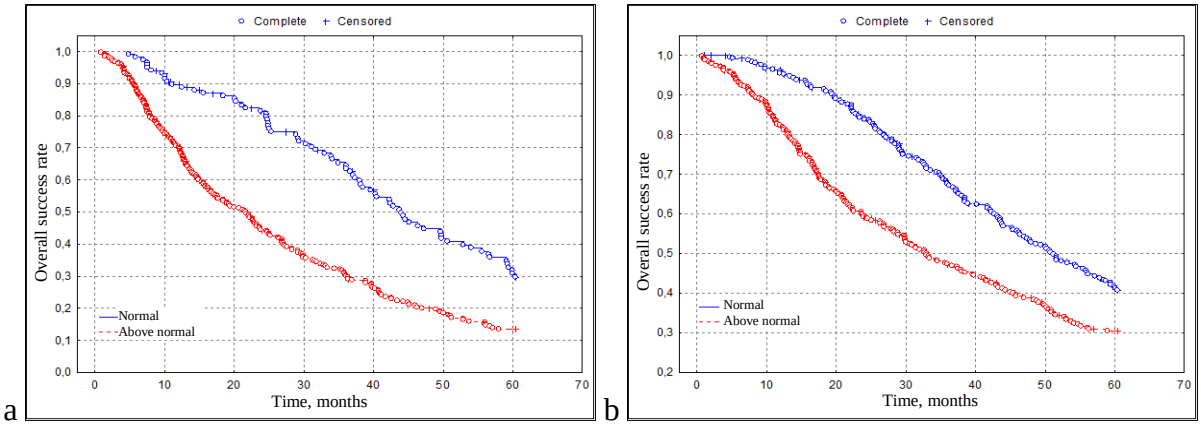


p<0,0001 p=0,09

Figure 4.37 – Comparison of OS indicators of patients with synchronous (a) and metachronous (b) metastases of RCC as a function of peripheral blood platelet count, with a normal platelet count of 150-400 units/μL

Thus, in patients with synchronous metastases of RCC, survival rates with normal platelets are higher than those with thrombocytosis (p<0.0001). At the same time, the number of peripheral blood platelets had no effect on the OS in patients with metachronous metastases of RCC (p=0.09).

Survival analysis showed that the 3- and 5-year OS of patients with normal ESR (2-15 mm/h) in RCC patients with synchronous and metachronous metastases were 60.2±1.6% and 30.8±1.5%, 66.7±1.5% and 41.1±1.6%, respectively. And the median OS was 43 and 51 months, respectively. And the 3-year and 5-year OS rates for elevated ESR (above 12-15 mm/h) of SM and MM patients were 29.5±1.5% and 13.4±1.3%, 47.8±1.5% and 30.4±1.5%, respectively Median OS 21 and 32 months, respectively (Figure 4.38).



p<0,0001

Figure 4.38 – Comparison of OS indicators of patients with synchronous (a) and metachronous (b) metastases of RCC depending on ESR, with normal ESR – 2-15 mm/h in women, 2-12 mm/h in men

Thus, in the present study, in patients with synchronous metastases of RCC, survival rates for normal ESR were significantly higher than those for elevated ESR ($p<0.0001$).

A Cox proportional hazards model was constructed to identify the effect of certain factors on survival (Table 4.39).

Table 4.39 shows that poor IMDC prognosis was the only significant prognostic factor in the group of metachronous metastases of RCC in single and multivariate analysis. In single-factor analysis of the OS parameters of the synchronous metastases subgroup, ESR and alkaline phosphate level were statistically significant Poor prognostic factors of the synchronous metastases of RCC group ($p<0.001$). In multivariate analysis, the same factors as in the group of metachronous metastases had a significant effect on the OB parameters.

Table 4.40 shows that for patients with metachronous metastases of RCC, poor prognosis according to IMDC was the only prognostic factor that had a significant effect on PFS. For the group of synchronous metastases, none of the factors had a significant effect on PFS.

Table 4.39 – Cox proportional hazards model of OB indicators in groups of synchronous and metachronous metastases of RCC

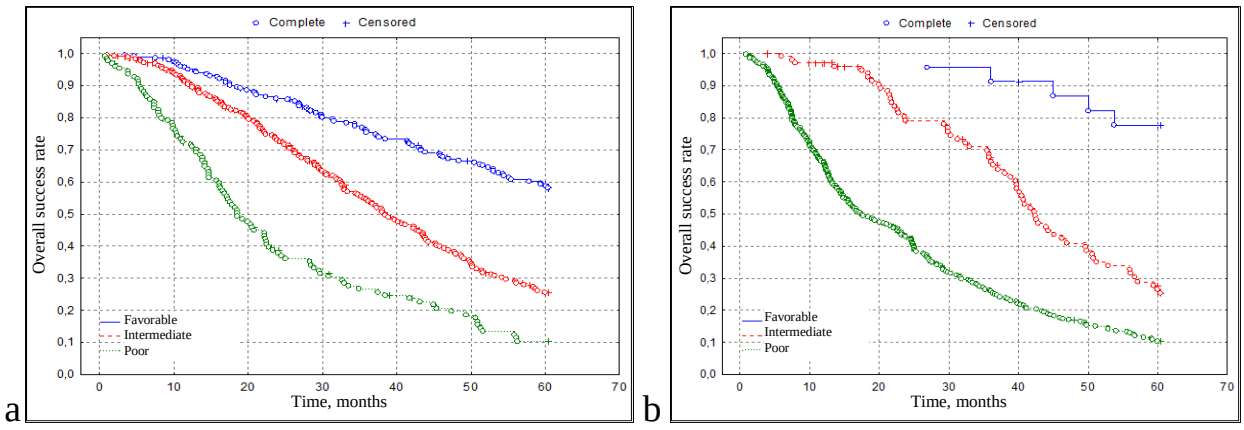
Signs		Synchronous mts RCC (N=403)				Metachronous mts of RCC (N=578)			
		single-factor		multifactorial		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
Forecast groups Heng	intermediate Poor	2.3 (1.7÷3.0)	<0.001	2.3 (1.8÷3.1)	<0.001	3.1 (2.4÷4.1)	<0.001)	2.8 (2.1÷3.8)	<0.001)
Gender	male	0.78 (0.6÷0.1)	=0.04	0.7 (0.5÷0.9)	=0.013	0.88 (0.7÷1.1)	=0.21	0.6 (0.4÷0.9)	0.007
	female								
Hemoglobin	norm	1.7 (1.5÷1.9)	<0.001	1.7 (1.5÷2.0)	<0.001	1.4 (1.3÷1.6)	<0.001	1.6 (1.4÷1.9)	<0.001
	Hb <NGH								
Neutrophils	norm	1.2 (1.03÷1.4)	=0.02	0.8 (0.5÷1.1)	=0.2	1.1 (0.8÷1.4)	0=.52	0.9 (0.6÷1.2)	=0.79
	Neu<NGN								
ESR	norm >ULN	2.1 (1.6÷2.8)	<0.001	1.3 (0.97÷1.8)	=0.08	1.4 (1.1÷1.8)	=0.014	0.96 (0.7÷1.3)	=0.81
Alkaline phosphatase	norm CF>ULN	1.5 (1.2÷1.9)	<0.001	0.9 (0.7÷1.2)	=0.39	1.4 (1.0÷1.8)	=0.03	1.1 (0.8÷1.5)	=0.56
LDH	norm	1.4 (1.1÷1.8)	=0.004	1.6 (1.2÷2.1)	=0.001	1.0 (0.8÷1.2)	=0.9	0.8 (0.6÷1.2)	=0.38
	>ULN								
Platelets	norm	1.2 (1.1÷1.4)	<0.01	0.98 (0.8÷1.2)	=0.1	1.0 (0.9÷1.1)	=0.9	1.0 (0.8÷1.3)	=0.9
	>ULN								

Table 4.40 – Cox proportional hazards model of PFS indicators in groups of synchronous and metachronous metastases of RCC

Signs		Synchronous mts RCC (N=403)				Metachronous mts of RCC (N=578)			
		single-factor		multifactorial		single-factor		multifactorial	
		hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value	hazard ratio (95% CI)	P-value
IMDC Forecast Groups	intermediate poor	1.2 (0.9÷1.7)	=0.10	1.2 (0.9÷1.6)	=0.18	2.7 (2.1÷3.6)	<0.001	2.7 (2.0÷3.6)	<0.001
Gender	male female	0.85 (0.7÷1.1)	=0.23	0.9 (0.7÷1.1)	=0.27	0.7 (0.5÷0.9)	=0.02	0.8 (0.6÷1.0)	=0.09
Hemoglobin	norm Hb <NGH	1.1 (1.0÷1.3)	=0.02	1.1 (1÷1.3)	=0.08	1.6 (1.4÷1.8)	0.001	1.6 (1.4÷1.9)	<0.001
Neutrophils	norm Neu<NGN	1.1 (0.8÷1.6)	0.65	0.9 (0.6÷1.4)	0.73	1.1 (07÷1.7)	0.66	0.9 (0.6÷1.5)	=0.76
ESR	norm >ULN	1.1 (0.9÷1.4)	=0.35	1.1 (0.8÷1.5)	=0.57	1.2 (0.9÷1.6)	=0.11	0.9 (0.6÷1.2)	=0.36
Alkaline phosphatase	norm CF>ULN	1.1 (0.9÷1.4)	=0.39	0.98 (0.8÷1.3	=0.91	1.2 (0.9÷1.6)	=0.13	1.1 (0.8÷1.5)	=0.64
LDH	norm >ULN	0.9 (0.7÷1.2)	=0.35	1.1 (0.8÷1.4)	=0.61	0.9 (0.7÷1.2)	=0.6	0.8 (0.5÷1.1)	=0.15
Platelets	norm	1.1 (0.9÷1.2)	=0.34	0.99 (0.8÷1.2)	=0.91	0.98 (08÷1.2)	=0.8	0.9 (0.8÷1.2)	=0.61

4.3.2 Comparison of patient survival rates with synchronous and metachronous renal cell cancer metastases according to IMDC prognosis

Survival analysis showed that 3-year and 5-year OS rates in the favorable prognosis group of patients with synchronous and metachronous metastases of RCC were 74.8±1.8% and 53.9±1.6%, 91.2±1.8% and 77.5±1.6%, respectively. And the OB rates in the intermediate prognosis group were 51.7±1.8% and 20.3±1.4%, 63.8±1.8% and 22.2±1.4% and in the Poor prognosis group were 27.4±1.8% and 8.2±1.3%, 27.5±1.7% and 8.3±1.3%, respectively. The median OV for favorable prognosis was not reached. The median OS at intermediate prognosis is 39 and 42 months, respectively. The median OS at poor prognosis 19 and 18 months, respectively (Figure 4.39).



p=0,0001

Figure 4.39 – Comparison of OS of patients with synchronous (a) and metachronous (b) metastases of RCC depending on IMDC prognosis

Thus, in our study, in patients with synchronous and metachronous metastases of RCC, there were significant differences in patients OS rates depending on IMDC prognosis (p=0.0001).

4.3.3 Comparison of survival rates of patients with synchronous and metachronous metastases of renal cell carcinoma IMDC intermediate forecast groups

The presented Kaplan-Meier curves (Figure 4.40) demonstrate that the 3-year and 5-year OS rates with synchronous and metachronous metastases of RCC in the presence of 1 adverse factor were 65.4±1.6% and 38.6±1.5%, 69.1±1.7% and 38.5±1.6%, respectively. Meanwhile, the median OS was 51 and 52 months, respectively. The 3-year and 5-year OS rates with metachronous metastases in RCC patients with 2 Poor factors were 39.8±1.6% and 14.6±1.3%, 38.6±1.6% and 12.3±1.5%, respectively. Median OS 40 and 30 months, respectively.

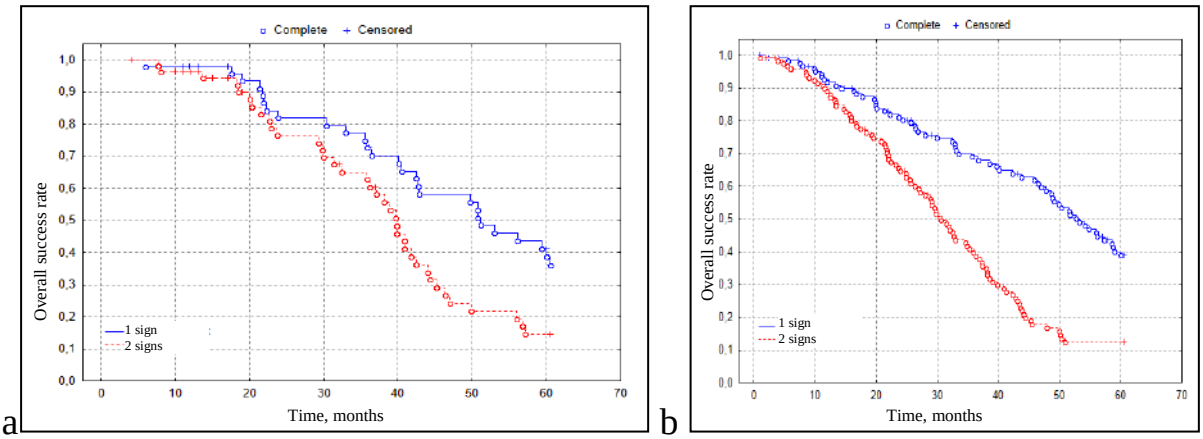


Figure 4.40 – Comparison of OS indicators of patients with synchronous and metachronous metastases of RCC with the presence of one (a) or two poor factors (b)

Differences in groups of synchronous and metachronous metastases of RCC patients are statistically significant ($p<0.001$), i.e. survival rates are much worse in the presence of 2 factors, especially in patients with synchronous metastases. Also in the work of M. Callea et al. noted that understanding of prognostic differences between synchronous and metachronous metastases of RCC is important for the development of treatment strategies for mRCC in the era of systemic therapy [85].

Conclusion

Thus, our study showed that the survival rates of mRCC patients are influenced by the number of affected organs and the time of their occurrence, localization of metastases, pathomorphological characteristics of the tumor and clinical and laboratory parameters. The study revealed statistically significant differences in OS and median OS depending on the number of affected organs (p=0.0008).

The localization of metastases and their number are important in the prognosis of patients with mRCC. Most often distant metastases were detected in lungs (66.8%), bones (35.7%) and lymph nodes (33.9%). It is clear that the localization of metastases determines the course and prognosis of mRCC. Lower 3- and 5-year OS rates were observed for isolated metastases in lung (44.5% and 27.6%), bone (37.4% and 11.9%), and lymph nodes (38.9% and 21.4%), respectively. In addition, such a characteristic of the tumor process as the number of metastases in mRCC patients turned out to be significant in terms of survival rates.

In addition, in patients with solitary metastases of RCC, light-cell highly differentiated carcinomas were detected in 35 (38.9%) patients, and in patients with multiple metastases, low-differentiated tumors were detected in 351 (55.0%) patients. In patients with metastases to the lungs, bones, and brain, luminal cell carcinomas were detected more frequently, and papillary cancer was found in liver lesions. Lymphogenic metastases were extremely rare in the G3 secular cell variant and in the G2 papillary variant. Metastases to the brain were detected only in G2 and G3 in 9.3% and 26.7% of cases. Depending on the histological variant and the degree of tumor differentiation, differences were found only for lymph node involvement. In 82.2% of patients with solitary metastases of RCC depending on the degree of tumor differentiation according to Fuhrman, highly and moderately differentiated tumors were revealed. Somatic status in patients with solitary metastases of RCC was good in 69.9% (ECOG 0-1), and 80% of patients had favorable or intermediate prognosis according to IMDC. In patients with visceral and non-visceral solitary metastases of RCC, no significant difference in OS was found.

In the single-factor Cox analysis, the degree of tumor differentiation according to Fuhrman, brain metastases and metastasectomy were the factors influencing the OS in patients with solitary metastases of RCC. In multivariate analysis according to Cox, the degree of tumor differentiation according to Fuhrman, brain metastases were the factors influencing the survival rates in patients with solitary metastases of RCC. Thus, the study of survival rates in patients with solitary metastases of RCC in multivariate analysis showed the influence of the degree of tumor differentiation according to Fuhrman, as well as the presence of brain metastases.

In patients with single metastases, the G1 and G2 light-cell variant of the tumor predominated, but the non-small-cell variant was more common. The liver was rarely involved, but lymph nodes were more frequently involved. Lung and bone remained the dominant localization of metastases. Isolated lesion of lungs and bones was found in patients with mRCC at G1-G3. The third place in terms of occurrence was a combined lesion of these localizations at G1, and at G2 – metastases to the adrenal gland. In patients with single metastases of non-small cell cancer, depending on the histologic variant and degree of differentiation, differences were revealed for adrenal and liver lesions. In chromophobe and papillary cancers adrenal glands were never affected, in non-small cell cancer rarely (somewhat more often in G1 tumors). In papillary cancer, metastases to the liver were found in 1/3 of patients. Highly and moderately differentiated tumors were detected in 73% of patients with single metastases of RCC depending on the degree of tumor differentiation according to Fuhrman, and 78% of patients had favorable or intermediate prognosis according to IMDC.

In single-factor Cox analysis, the degree of tumor differentiation according to Fuhrman, bone and lung metastases, elevation of ESR and alkaline phosphatase, and performance of metastasectomy were the factors influencing the OS in patients with single metastases of RCC. In Cox multivariate analysis, the type of metastases, brain metastases, LDH elevation, and metastasectomy were the factors influencing the survival rates in patients with single metastases of RCC. Thus, the study of survival

rates in patients with single metastases of RCC in multivariate analysis showed the influence of the type of metastases, LDH level, and the presence of brain metastases.

G2-G3 variants of clear cell cancer predominated in patients with multiple metastases of RCC. There were also other histologic variants, more often low-differentiated. In patients with non-small cell cancer localization of metastatic lesions in lungs was 77-86%, bones – 50%, lymph nodes – 50-55%, liver – 26-33% and kidneys – 7.3-11.5%. In patients with non-small cell cancer, lung lesions were 50-70%, liver 40%, bone 25-33%, lymph nodes 33% and kidney 20-28%. There was an increase in liver and kidney involvement in non-small cell cancer. Adrenal gland involvement was rare, but a high percentage of lesions in G2 non-small cell cancer (19.2%) and papillary cancer (17.6%) drew attention. Low-differentiated tumors were detected in 55% of patients with multiple metastases of RCC depending on the degree of tumor differentiation according to Fuhrman. Somatic status in patients with solitary metastases was low in 63% (ECOG 2-3), and 52.4% of patients had poor prognosis according to IMDC.

In single-factor Cox analysis, tumor histologic variant, Fuhrman tumor differentiation degree, type of metastases, bone, lung, and liver metastases; elevated alkaline phosphatase, LDH, and ESR, as well as performance of CN, metastasectomy, and radiation therapy were the factors influencing the OS in patients with multiple metastases of RCC. At multivariate analysis according to Cox, tumor histological variant, tumor differentiation degree according to Fuhrman, type of metastases, metastases to the brain, as well as performance of CN, metastasectomy were the factors influencing the survival rates in patients with multiple metastases of RCC. Thus, the study of survival rates in patients with multiple metastases of RCC in multivariate analysis showed the influence of tumor histological variant, tumor differentiation degree according to Fuhrman and type of metastases, performance of CN and metastasectomy, as well as the presence of brain metastases**.**

We further studied the dependence of survival rates in patients with synchronous and metachronous metastases of RCC. Lesions of 1 and 2 organs were more frequently observed in patients with metachronous metastases, and multiorgan

lesions were found in synchronous metastases. OS indices differed in patients with synchronous and metachronous metastases of RCC. Patients with synchronous metastases more often had poor prognosis according to IMDC and ECOG status, low degree of differentiation, presence of lymphogenic metastases and a greater number of organs affected by metastases. Anemia and elevated ESR were more frequently observed in patients with synchronous metastases, while patients with metachronous metastases had normal platelet counts and alkaline phosphatase.

The results of our study showed that despite the existing tendency of prevalence of metastases to lungs, bones and lymph nodes, histological variants, the degree of tumor differentiation and laboratory data impose an imprint on the peculiarities of the metastatic process, which should be taken into account in the approach to the prescription of systemic therapy.

Chapter 5
EVALUATING FORECAST AND THEIR INFLUENCE ON THE EFFICACY OF CYTOREDUCTIVE SURGERY IN PATIENTS WITH METASTATIC RENAL CELL CANCER

5.1 Evaluation of forecast factors and their impact on efficiency when performing cytoreductive nephrectomy in patients with metastatic renal cell cancer

In our study, 330 patients with mRCC underwent cytoreductive nephrectomy.

We considered clinical, laboratory, and pathomorphologic factors influencing the OS indices of patients with mRCC who underwent CN. At present, the factor of cytoreductive surgery in mRCC is considered as a factor of favorable prognosis. However, there is no clear understanding of what factors should be taken into account when performing CN in mRCC patients and whether there is a separate group of patients who do not need to undergo it.

5.1.1 Survival rates of patients depending on the from clinical characteristics in the performance of cytoreductive nephrectomy

Figure 5.1 shows that the rates of 3- and 5-year OS in patients at CEN 3 and 5-year OS were 48.2±1.6% and 11.3±1.4%, respectively. At the same time, the median OS was 32 months.

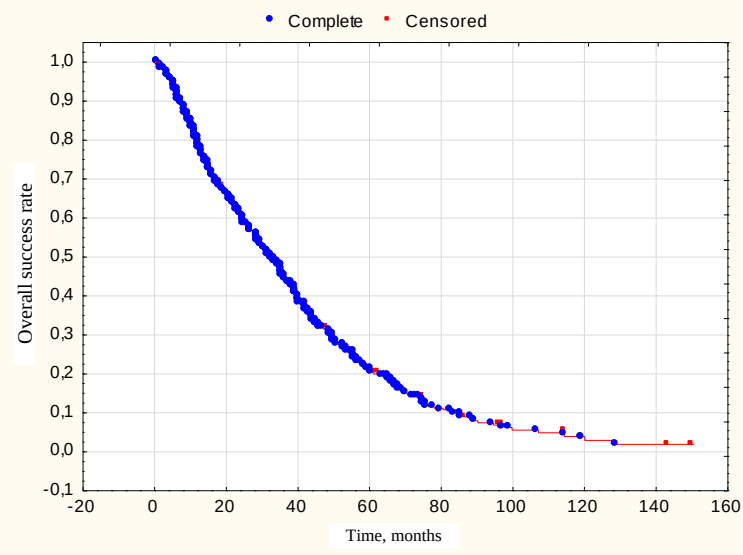


Figure 5.1 – Kaplan-Meier curve of the OS index of mRCC patients (N=330) when performing CN

To assess the influence of different prognostic factors on the OS parameters in mRCC patients, stratification of patients into different prognostic groups was performed.

The mean age of the patients was 59±9.6 years (22 years – 82 years). Less than 60 years – 163 (48.4%) and more than 60 years – 167 (50.6%) patients. When evaluating the mRCC patients included in the study, it was found that the study was dominated by patients in the age range of 45-59 years at 44.8% (Table 5.1).

Table 5.1 – Distribution of mRCC patients at CN according to age

Age	Number of patients	HR
18-44	19 (5.8)	–
45-59	148 (44.8)	1.38 (0.76-2.50, p=0.288)
60-74	143 (43.3)	1.21 (0.67-2.19, p=0.533)
over 75	20 (6.1)	1.73 (0.83-3.61, p=0.143)

Figure 5.2 shows that the rates of 3- and 5-year OS of patients according to age were at age 18-44 years were 59.86% [39.119-91.59%, 95% CI] and 17.10% [4,919-59.46%, 95% CI], at age 45-59 years were 46.22% [38.704-55.20%, 95% CI] and

20.33% [14.581-28.34%, 95% CI], at age 60-74 years were 46.69% [39.044-55.83%, 95% CI] and 24.17% [17.855-32.71%, 95% CI]. And in patients older than 75 years, 37.06% [20.612-66.63%, 95% CI] and 10.59% [2.857-39.24%, 95% CI], respectively. The median OS was 42.9 [26.3-NA, 95% CI] 31.9 [25-38.9, 95% CI], 32.9 [27.6-40.8, 95% CI], and 31.1 [13.7-46.3, 95% CI] months, respectively.

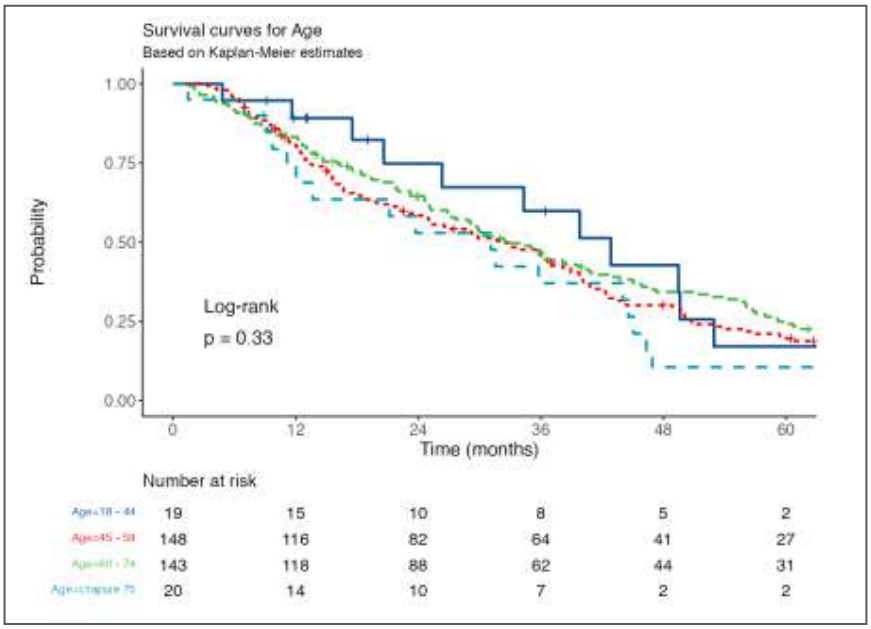


Figure 5.2 – Kaplan-Meier curves of OS indicators of mRCC patients (N=330) when performing CN as a function of age

Thus, there is no advantage in the rates of OS and median OS according to age in mRCC patients when performing CN (p=0.33).

When evaluating the mRCC patients in performing CN included in the study, it was found that males predominated in 72.4% of cases in the study (Table 5.2).

Table 5.2 – Distribution of mRCC patients at CN according to gender characteristics

Gender	Number of patients	HR
Men	239 (72.4)	–
Women	91 (27.6)	0.77 (0.59-1.00, p=0.053)

The results of calculating survival rates according to gender are presented in Figure 5.3.

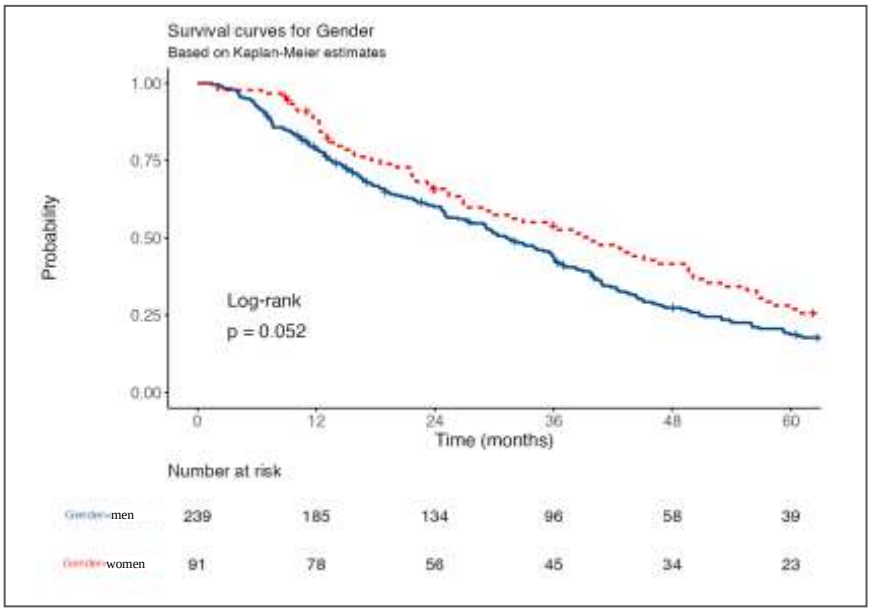


Figure 5.3 – Kaplan-Meier curves of OS indicators in mRCC patients (N=330) when performing CN depending on gender characteristics

Survival analysis found that the 3- and 5-year OS rates of mRCC patients at CN in men were 43.8% [37.8-51%, 95% CI] and 18.8% [14.2-25%, 95% CI], and in women 53.9% [44.3-66%, 95% CI] and 28.2% [20.0-40%, 95% CI], respectively, With a median OS of 31.3 [27.1-36.1, 95% CI] and 39.8 [29.3-49.8, 95% CI] months, respectively. Thus, in this study, there was no advantage in OS and median OS according to gender in mRCC patients when performing CN (p=0.052).

In the patients included in the study, the frequency of kidney involvement was approximately equal: left kidney tumor was detected in 157 (47.6%) patients, right kidney tumor was detected in 164 (49.7%) patients, bilateral involvement was diagnosed in 9 (2.7%) patients, as shown in Table 5.3.

Table 5.3 – Distribution of mRCC patients undergoing CN depending on the localization of the renal tumor

Localization of the primary tumor	Number of patients	HR
On the right	157 (47.6)	–
From left	164 (49.7)	0.94 (0.75-1.19, p=0.628)
Bilateral	9 (2.7)	0.84 (0.39-1.79, p=0.643)

Figure 5.4 shows that the 3-year and 5-year OS rates depending on the location of the patients' primary kidney tumor were 49.1% [41.8-57.6%, 95% CI] and 22,3% [16.5-30.1%, 95% CI], on the right – 43.7% [36.4-52.5%, 95% CI] and 20.5% [14.9-28.3%, 95% CI], with both kidneys affected – 51.9% [26.7-100.0%, 95% CI] and 17.3% [3.1-97.8%, 95% CI], respectively. Meanwhile, the median OS was 31.6 [25-38.1, 95% CI], 35 [26.9-40.8, 95% CI], and 42.9 [27.2-NA, 95% CI] months, respectively. Thus, the study revealed no statistically significant differences in OS and median OS depending on the side of the primary tumor lesion in mPCC patients at CEN (p=0.82).

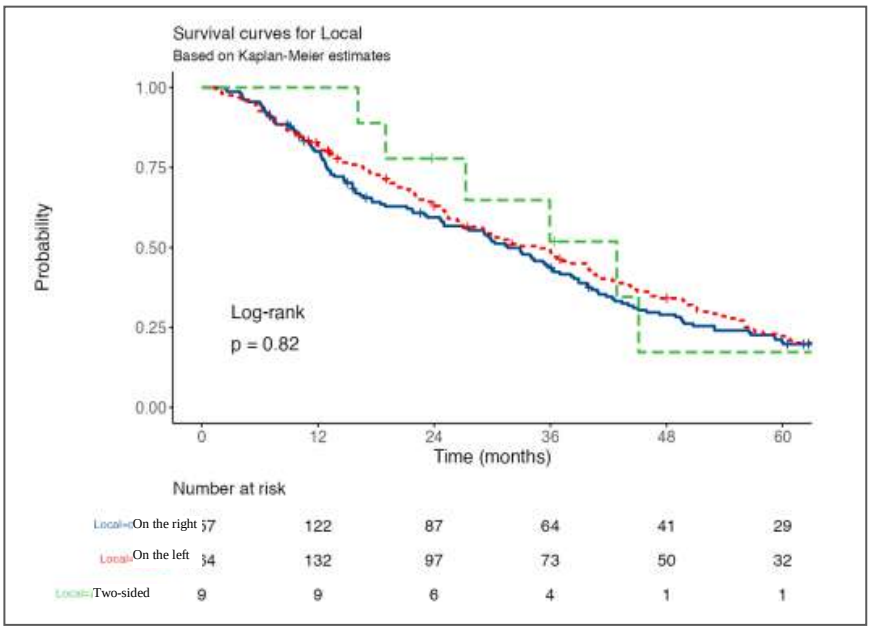


Figure 5.4 – Kaplan-Meier curves of OS indicators in mRCC patients (N=330) when performing CN depending on the side of the primary tumor involved

When evaluating the mRCC patients in performing CN included in the study according to ECOG status, Table 5.4 shows that patients with ECOG 1-2 somatic status predominated in 69.7% of cases.

Table 5.4 – Distribution of mRCC patients undergoing CN depending on ECOG status

ECOG status	Number of patients	HR
ECOG0	9 (2.7)	–
ECOG1	105 (31.8)	1.52 (0.48-4.83, p=0.475)
ECOG2	125 (37.9)	3.67 (1.16-11.61, p=0.027)
ECOG3	91 (27.6)	18.83 (5.85-60.62, p<0.001)

The presented Kaplan-Meier curves (Figure 5.5) demonstrated that the 3-year and 5-year OS rates of patients with ECOG0 status were 75.00% [42.59-100.0%, 95% CI] and 50.00% [18.77-100.0%, 95% CI], with ECOG1 status were 82,49% [75.25-90.4%, 95% CI] and 45.93% [36.75-57.4%, 95% CI], at ECOG2 – 45.55% [37.47-55.4%, 95% CI] and 16.03% [10.62-24.2%, 95% CI], and at ECOG3 – 47.25% [38.03-58.7%, 95% CI] and 6.59% [3.04-14.3%, 95% CI], respectively. Meanwhile, the median OS at ECOG 0, 1, 2, 3 was 78.3 [32.4-NA, 95% CI] 57.9 [53-68.7, 95% CI], 34.1 [29.8-38.9, 95% CI], and 11.2 [9.5-12.9, 95% CI] months, respectively.

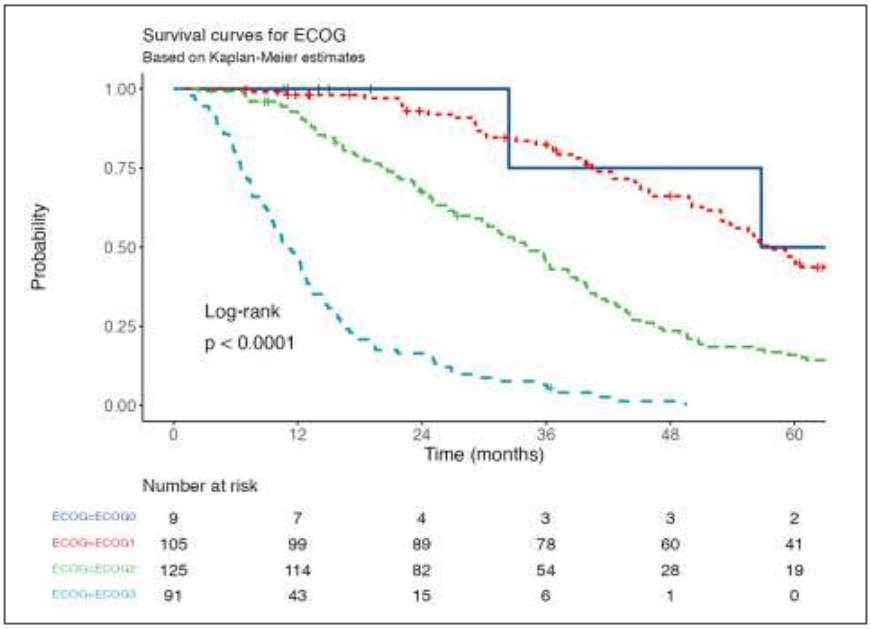


Figure 5.5 – Kaplan-Meier curves of OS indicators in mRCC patients when performing CN depending on ECOG status (N=330)

Thus, the study revealed statistically significant differences in the rates of OS and median OS in mRCC patients when performing CN depending on ECOG status ($p<0.0001$).

Although we consider the factors included in the IMDC prognostic model separately, we evaluated the survival rates of patients undergoing CN in 3 prognostic groups in the overall cohort. Table 5.5 shows that of the 330 patients who underwent CN, 21 (6.4%) were in the favorable prognosis group, 90 (27.3%) in the intermediate prognosis group, and 219 (66.3%) in the poor prognosis group. Thus, more than 90% of patients were from the intermediate and poor prognosis groups according to IMDC.

Table 5.5 – Distribution of mRCC patients undergoing CN depending on IMDC prognosis

IMDC Forecast	Number of patients	HR
Favorable	21 (6.4)	–
Intermediate	90 (27.3)	4.05 (2.05-7.99, p<0.001)
Poor	219 (66.4)	8.59 (4.46-16.56, p<0.001)

The presented Kaplan-Meier curve diagram (Figure 5.6) shows that OS rates directly depend on IMDC prognosis. Thus, in the favorable prognosis group, the 3- and 5-year OS rates of patients were 100.00% [100.0-100.00%, 95% CI] and 80.20% [64.6-99.63%, 95% CI], while in the intermediate prognosis group 72,41% [63.2-82.94%, 95% CI] and 28.18% [19.6-40.42%, 95% CI], And the OS rates in the poor prognosis group were 31.08% [25.4-38.00%, 95% CI] and 12.64% [8.8-18.15%, 95% CI], respectively. Meanwhile, the median OS also differed and was 99.8 [89.4-NA, 95% CI], 42.9 [40.4-51.1, 95% CI], and 23 [17.3-26.5, 95% CI] months, respectively.

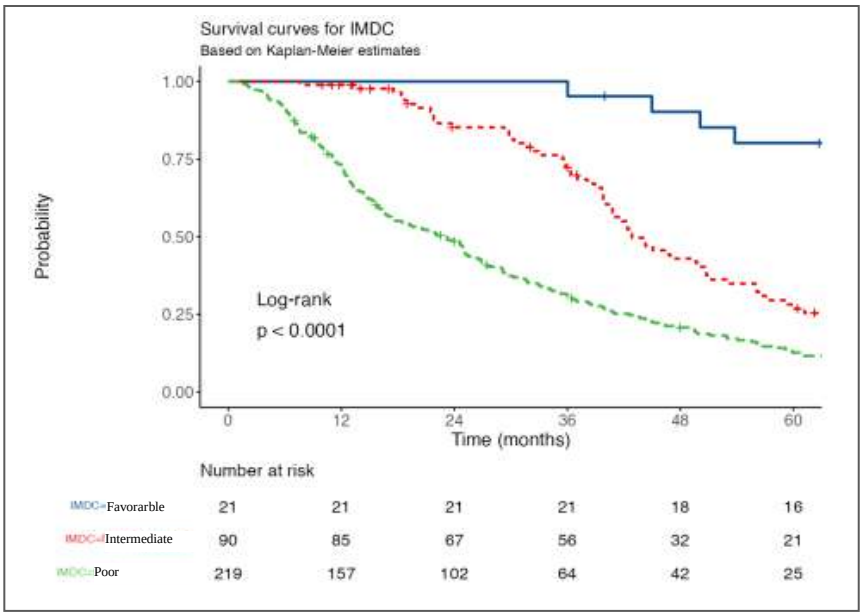


Figure 5.6 – Kaplan-Meier curves of OS indicators in mRCC patients when performing CN depending on IMDC prognosis (N=330)

In summary, the study revealed statistically significant differences in OS and median OS depending on IMDC prognosis in mRCC patients undergoing CN ($p<0.0001$).

5.1.2 Influence of tumor morphological characteristics on survival rates in patients with metastatic renal cell carcinoma in cytoreductive nephrectomy with tumor morphologic characteristics

When evaluating the mRCC patients included in the study depending on the histologic variant in the majority of cases, 279 (84.5%) patients were verified as having clear cell carcinoma. Non-small cell variants accounted for 51 (15.5%) cases (Table 5.6).

Table 5.6 – Distribution of mRCC patients undergoing CN depending on the histological subtype of the primary tumor

Histologic variant	Number of patients	HR
Clear-cell	279 (84.5)	–
Non-small cell	51 (15.5)	2.00 (1.46-2.73, p<0.001)

The presented Kaplan-Meier curve plot (Figure 5.7) shows that the 3-year and 5-year OS rates for clear-cell tumor were 50.4% [44.7-56.8%, 95% CI] and 24.5% [19.7-30.5%, 95% CI], and for non-small cell cancer were 26.3% [16.5-41.9%, 95% CI] and 4.4% [1.1-16.9%, 95% CI], respectively. Meanwhile, the median OS also differed and was 36.1 [31.6-40.3, 95% CI] and 21.2 [12.7-29.5, 95% CI] months, respectively.

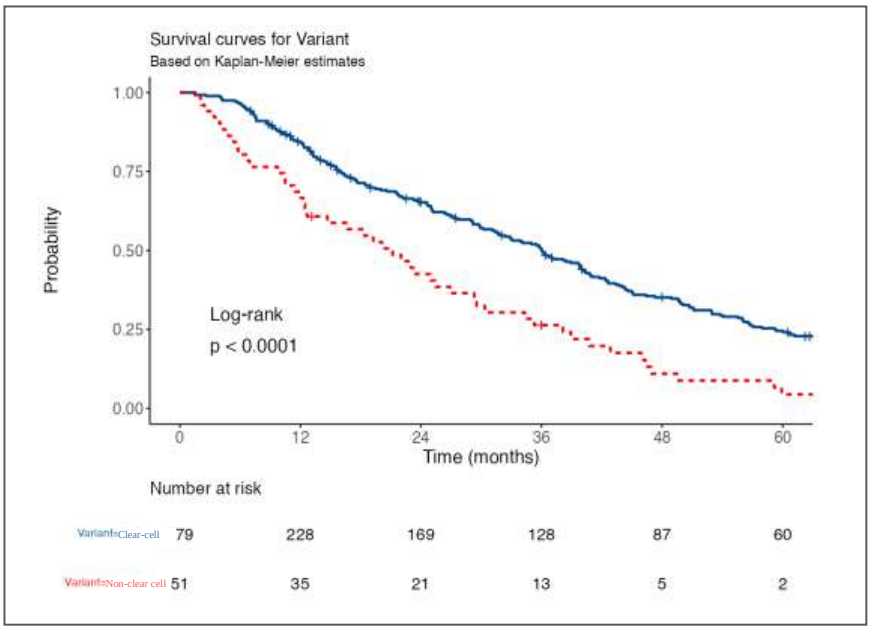


Figure 5.7 – Kaplan-Meier curves of OS indices of mRCC patients (N=330) depending on the histological variant of the tumor when performing CN

Thus, the study revealed statistically significant differences in OS and median OS rates depending on the histologic subtype of tumor in mRCC patients, with the clear-cell variant being the most favorable (p<0.0001).

When evaluating the patients with mRCC included in the study depending on the degree of differentiation according to Fuhrman were distributed as follows. Table 5.7 shows that the number of patients at G1 was 17 (5.1%), at G2 – 103 (31.2%) and G3 – in 210 (63.7%) patients, respectively. Thus, more than 60% of patients had low-differentiated tumors.

Table 5.7 – Distribution of mRCC patients at CN depending on the degree of tumor differentiation according to Fuhrman

Degree of differentiation according to Fuhrman	Number of patients	HR
Grade 1	17 (5.2)	–
Grade 2	103 (31.2)	2.84 (1.51-5.36, p=0.001)
Grade 3	210 (63.6)	5.23 (2.83-9.70, p<0.001)

Depending on tumor differentiation according to Fuhrman (Figure 5.8), the 3-year and 5-year OS rates were 94.1% [83.6-100.000%, 95% CI] and 88.2% [74.2-100.000%, 95% CI], 63.6% [54.7-74.042%, 95% CI] and 30.4% [22.3-41.481%, 95% CI], 34.2% [28.2-41.526%, 95% CI] and 10.9% [7.2-16.446%, 95% CI], respectively. Meanwhile, the median OS also differed significantly according to the degree of tumor differentiation and was 89 [78-NA, 95% CI], 44.3 [38.9-50.1, 95% CI], and 24.6 [18.4-29.2, 95% CI] months, respectively.

Thus, our study revealed statistically significant differences in the OS and median OS of mRCC patients when performing CN depending on the degree of tumor differentiation according to Fuhrman ($p<0.0001$).

Solitary metastases were detected in 16 (4.8%) patients, single metastases in 65 (19.7%) and multiple metastases in 249 (75.5%) patients (Table 5.8).

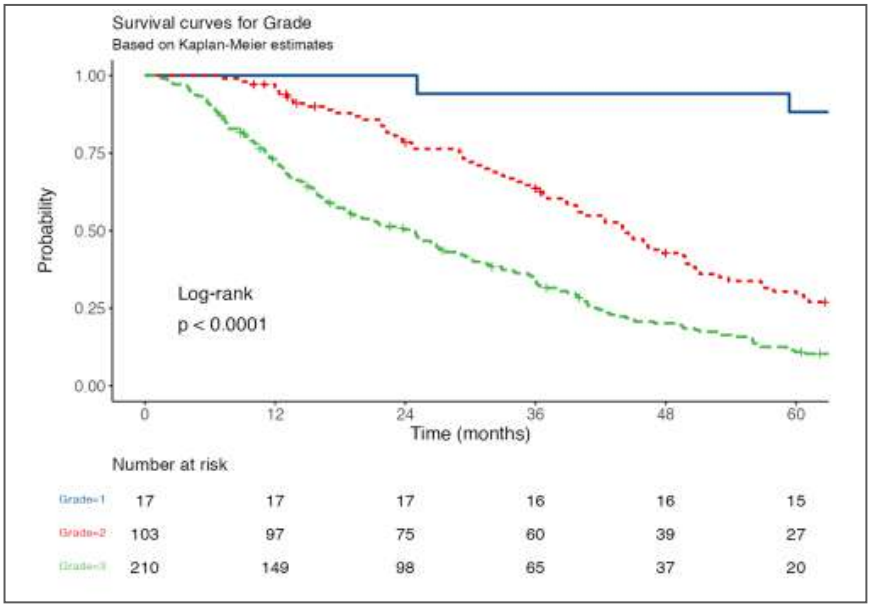


Figure 5.8 – Kaplan-Meier curves of OS indicators of mRCC patients when performing CN (N=330) depending on tumor differentiation according to Fuhrman

Table 5.8 – Distribution of mRCC patients undergoing CN depending on the number of metastases

Number of metastases	Number of patients	HR
Solitary	16 (4.8)	–
Single	65 (19.7)	0.98 (0.53-1.81, p=0.955)
Multiple	249 (75.5)	3.25 (1.84-5.75, p<0.001)

As shown in Figure 5.9, the survival rates directly depend on the number of metastases. Thus, in patients with solitary, single, and multiple metastases with CN, the 3- and 5-year OS rates were 75,0% [56.5-99.52%, 95% CI] and 56.2% [36.5-86.66%, 95% CI], 84.3% [75.8-93.73%, 95% CI] and 49.3% [38.4-63.34%, 95% CI], 34.3% [28.7-41.04%, 95% CI] and 10.8% [7.4-15.96%, 95% CI], respectively. Meanwhile, the median OS was 70.9 [38.9-NA, 95% CI], 56.5 [52.9-74.1, 95% CI], and 25 [21.5-29.8, 95% CI] months, respectively.

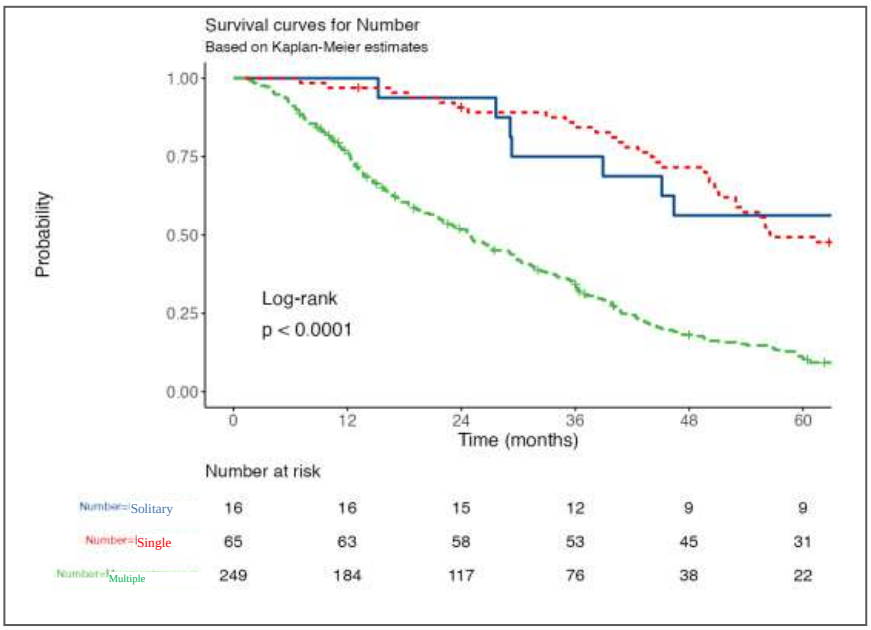


Figure 5.9 – Kaplan-Meier curves of OS indices of mRCC patients (N=330) when performing CN depending on the number of metastases

Thus, the conducted study revealed statistically significant differences in the rates of OS and median OS in mRCC patients when performing CN depending on the number of metastases ($p<0.0001$).

5.1.3 Impact of laboratory data on survival rates of patients with metastatic renal cell cancer when performing cytoreductive nephrectomy

When evaluating the patients included in the study depending on the hemoglobin level were distributed as follows. Thus, normal hemoglobin level was noted in 209 (63.3%) patients and anemia was noted in 121 (36.7%) patients. Thus, one-third of the mRCC patients in our study had anemia, as shown in Table 5.9.

As shown in Figure 5.10, the 3-year and 5-year OS rates for normal hemoglobin were 64.6% [58.2-71.7%, 95% CI] and 29.1% [23.2-36.4%, 95% CI]. In anemia, these rates decreased significantly to 16.1% [10.6-24.2%, 95% CI] and 8.2% [4.5-15.1%, 95% CI], respectively. The median OS also differed according

to hemoglobin level and was 42.6 [39.8-48.9, 95% CI] and 13.3 [12.2-16.1, 95% CI] months, respectively.

Table 5.9 – Distribution of mRCC patients under CN depending on hemoglobin level

Hemoglobin level	Number of patients	HR
Hemoglobin's normal	209 (63.3)	–
Anemia	121 (36.7)	2.93 (2.30-3.73, p<0.001)

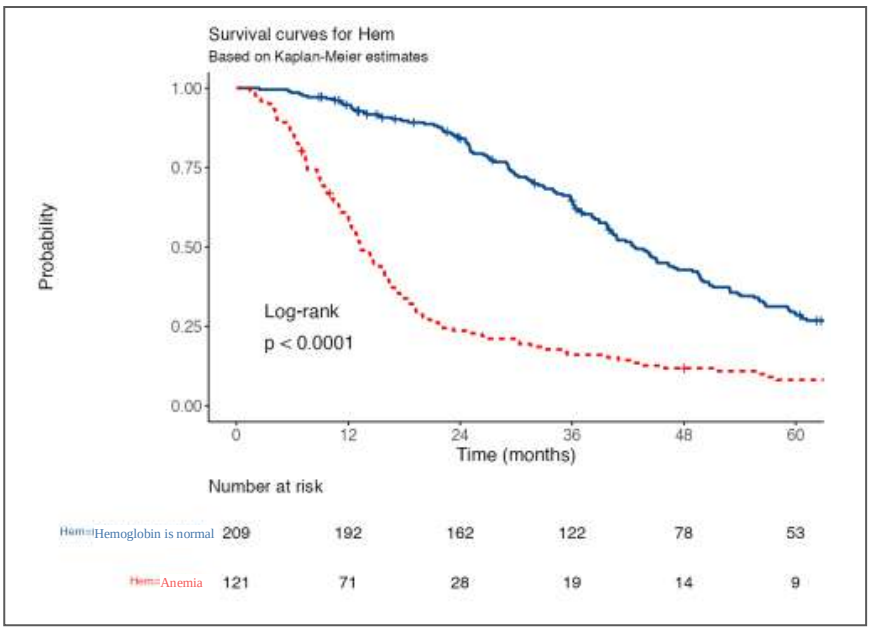


Figure 5.10 – Comparison of OS indicators of mRCC patients (N=330) when performing CN depending on hemoglobin levels

Thus, the conducted study revealed statistically significant differences in OS and median OS depending on hemoglobin level in mRCC patients when performing CN (p<0.0001).

When evaluating the patients included in the study depending on the level of alkaline phosphorus were distributed as follows. Thus, as can be seen from Table 5.10, a normal level of alkaline phosphorus was detected in 213 (64.5%) patients, and elevation of this index was noted in 117 (35.5%) patients. Thus, 2/3 of patients with mRCC had normal alkaline phosphorus levels.

Table 5.10 – Distribution of mRCC patients at CN depending on the level of alkaline phosphorus

Alkaline phosphatase	Number of patients	HR
alkaline phosphorus is normal	213 (64.5)	–
alkaline phosphorus is elevated	117 (35.5)	1.32 (1.03-1.68, p=0.027)

The presented Kaplan-Meier curves (Figure 5.11) show that the 3-year and 5-year OS were 53.1% [46.6-60.4%, 95% CI] and 23.7% [18.4-30.5%, 95% CI], 34.7% [26.8-44.9%, 95% CI], and 17.0% [11.1-26.0%, 95% CI] for normal and elevated alkaline phosphorus, respectively. Meanwhile, the median OS also differed according to alkaline phosphate levels and was 37.1 [31.9-41, 95% CI] and 23.2 [17.6-32.9, 95% CI] months, respectively.

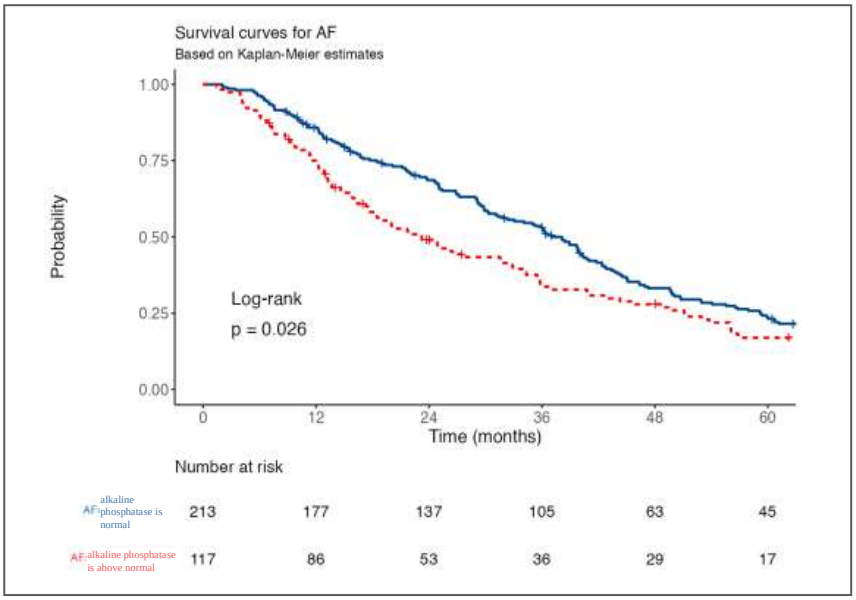


Figure 5.11 – Comparison of OS indicators of patients with mRCC (N=330) when performing CN depending on the level of alkaline phosphorus

Thus, the study revealed statistically significant differences in OS and median OS depending on the level of alkaline phosphate in mRCC patients when performing CN (p=0.026).

When evaluating the patients included in the study depending on LDH level were distributed as follows. Thus, 243 (73.6%) patients had normal LDH levels, and elevation of this index was noted in 87 (26.4%) patients, which is shown in Table 5.11. Thus, more than 70% of mRCC patients had normal LDH levels.

Table 5.11 – Distribution of mRCC patients at CN depending on LDH level

LDH level	Number of patients	HR
LDH is normal	243 (73.6)	–
LDH is elevated	87 (26.4)	1.35 (1.04-1.76, p=0.023)

The presented Kaplan-Meier curves (Figure 5.12) show that the 3-year and 5-year OS rates for normal and elevated LDH were 50% [44.3-57.3%, 95% CI] and 24% [19.0-30.4%, 95% CI], 36% [27.1-48.0%, 95% CI] and 14% [7.8-24.0%, 95% CI], respectively. The median OS also differed by LDH level and was 36 [30.4-40.3, 95% CI] and 22 [16.7-34.3, 95% CI] months, respectively.

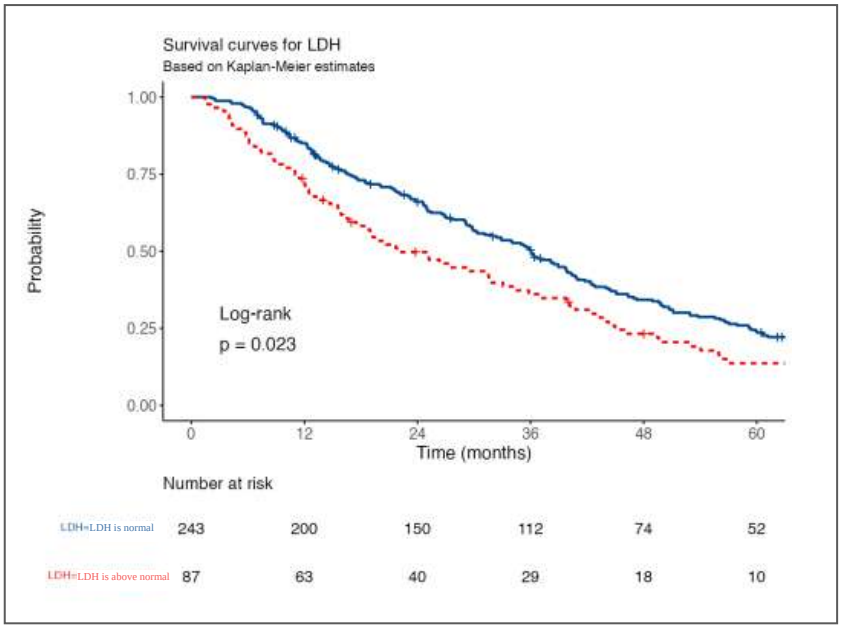


Figure 5.12 – Comparison of OS indicators of patients with mRCC (N=330) when performing CN depending on LDH level

Thus, the conducted study revealed statistically significant differences in OS and median OS depending on LDH level in mRCC patients when performing CN (p=0.023).

5.1.4 Influence of metastases localization on survival rates of patients with metastatic renal cell cancer when performing cytoreductive nephrectomy

The distribution of mRCC patients undergoing CN depending on the presence of bone metastases is presented in Table 5.12.

Table 5.12 – Distribution of mRCC patients under CN depending on the presence of bone metastases

Bone metastasis	Number of patients	HR
Bone metastasis (-)	195 (59.1)	–
Bone metastases (+)	135 (40.9)	1.05 (0.83-1.33, p=0.681)

The presented Kaplan-Meier curves (Figure 5.13) show that the 3-year and 5-year OS rates were 50.26% [43.54-58.01%, 95% CI] and 21.76% [16.46-28.76%, 95% CI] in the absence of bone metastases, and 41.32% [33.59-50.83%, 95% CI] and 20.79% [14.67-29.48%, 95% CI] in the presence of bone metastases, respectively. Meanwhile, the median OS was 36 [29.3-40.3, 95% CI] and 31.3 [23.2-36.3, 95% CI] months, respectively. Thus, the study showed no statistically significant differences in OS and median OS in mRCC patients with CN and absence/presence of bone metastases (p=0.68).

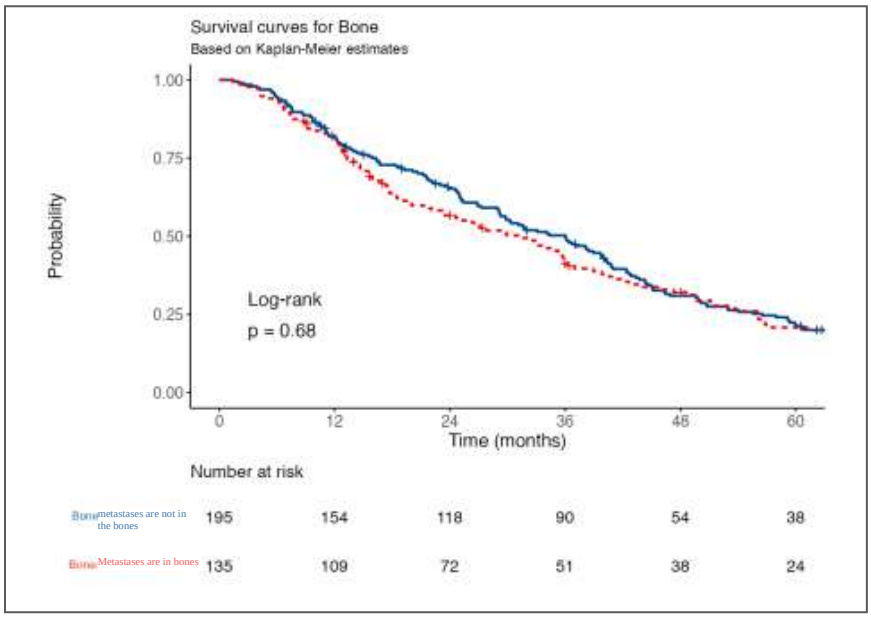


Figure 5.13 – Comparison of OS indicators of mRCC patients with absence/presence of bone metastases at CEN (N=330)

The distribution of mRCC patients undergoing CN depending on the presence of lung metastases is presented in Table 5.13.

Table 5.13 – Distribution of mRCC patients at CN depending on the presence of lung metastases

Lung metastasis	Number of patients	HR
Lung metastases (-)	107 (32.4)	–
Lung metastases (+)	223 (67.6)	1.10 (0.86-1.41, p=0.442)

Figure 5.14 shows that the 3-year and 5-year OS rates in the absence of lung metastases were 49.5% [40.81-60.1%, 95% CI] and 23.3% [16.34-33.2%, 95% CI], and in the presence of lung metastases were 45.1% [38.83-52.4%, 95% CI] and 20.4% [15.46-26.8%, 95% CI], respectively. The median OS was 35.8 [26.5-44.3, 95% CI] and 31.6 [27.1-36.4, 95% CI] months, respectively.

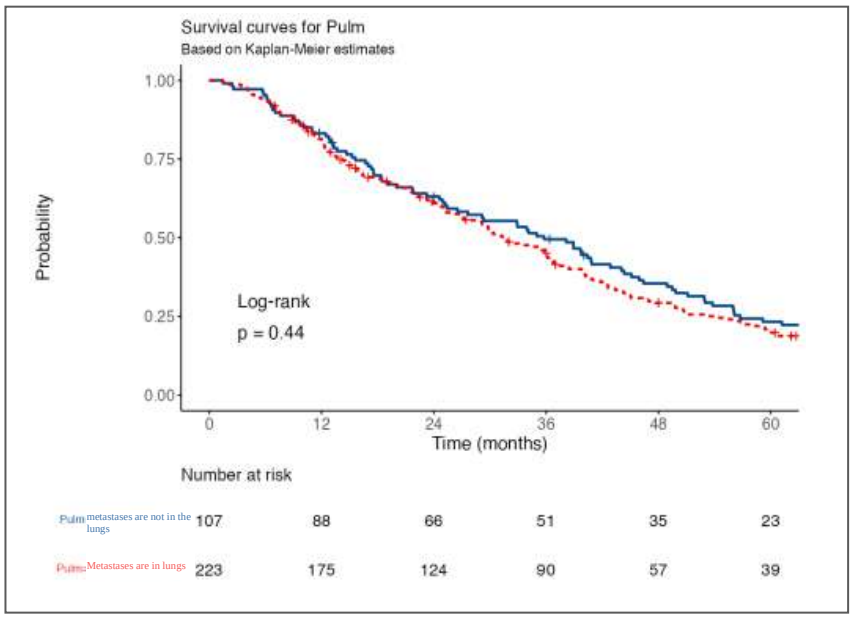


Figure 5.14 – Comparison of OS indicators of mRCC patients with absence/presence of bone metastases at CEN (N=330)

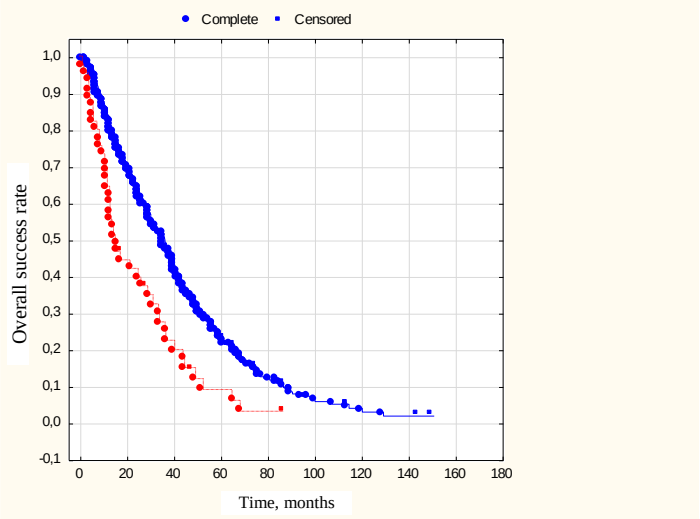
Thus, the study showed no statistically significant differences in the rates of OS and median OS in mRCC patients when performing CN and absence/presence of bone metastases (p=0.44).

The distribution of mRCC patients undergoing CN depending on the presence of liver metastases is presented in Table 5.14.

Table 5.14 – Distribution of mRCC patients undergoing CN depending on the presence of liver metastases

Metastasis to the liver	Number of patients	HR
Metastasis to the liver (-)	285 (86.4)	–
Metastasis to the liver (+)	45 (13.6)	1.89 (1.35-2.65, p<0.001)

The presented Kaplan-Meier curves (Figure 5.15) show that the 3-year and 5-year OS rates in the absence of liver metastases were 51.5±1.6% and 22.3±1.4%, and in the presence of liver metastases were 27.5±1.4% and 9.4±1.3%, respectively. The median OS also differed according to the absence/presence of liver metastases and was 37 and 17 months, respectively.



p=0,002

Figure 5.15 – Comparison of OS indicators of mRCC patients with absence/presence of liver metastases at CN (N=330)

Thus, the study revealed statistically significant differences in the rates of OS and median OS in mRCC patients when performing CN and absence/presence of liver metastases (p=0.002).

The distribution of mRCC patients undergoing CN depending on the presence of lymph node metastases is presented in Table 5.15.

Table 5.15 – Distribution of mRCC patients undergoing CN depending on the presence of metastases to lymph nodes

Metastasis to Lymph nodes	Number of patients	HR
Metastases to lymph nodes (-)	174 (77.0)	–
Metastases to lymph nodes (+)	52 (23.0)	1.03 (0.71-1.48, p=0.894)

Figure 5.16 shows that the 3-year and 5-year OS of patients in the absence of lymph node metastases were 60.7% [53.7-68.65%, 95% CI] and 44.0% [36.9-52.40%, 95% CI], and in the presence of lymph node metastases were 58.1% [45.5-74.20%, 95% CI] and 41.2% [28.9-58.68%, 95% CI], respectively. The median OS

also differed according to the absence/presence of lymph node metastases and was 51.5 [40.9-65.2, 95% CI] and 47.9 [34.1-70.6, 95% CI] months, respectively.

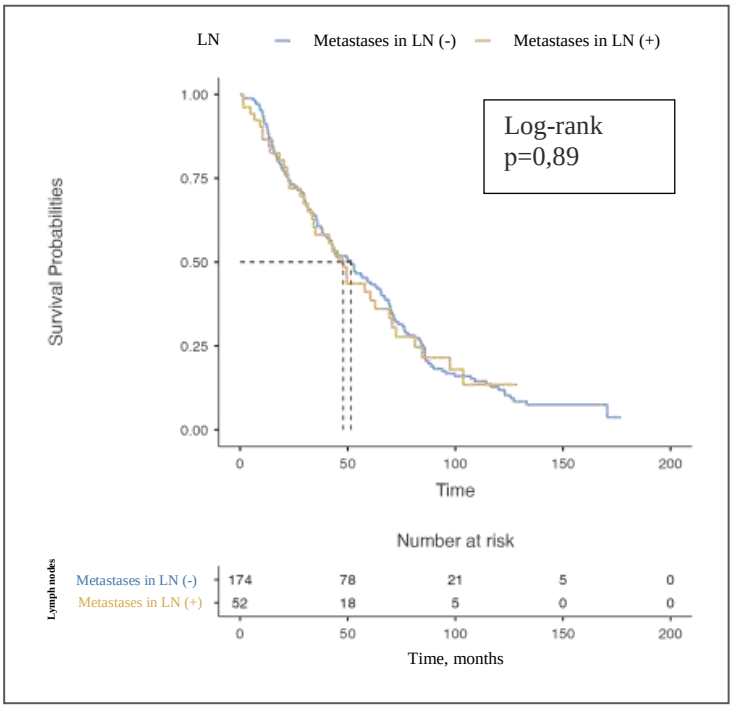


Figure 5.16 – Comparison of OS indicators of mRCC patients with absence/presence of metastases to lymph nodes when performing CN (N=330)

Thus, the conducted study revealed no statistically significant differences in OS and median OS in mRCC patients when performing CN and absence/presence of metastases to lymph nodes (p=0.89).

The distribution of mRCC patients undergoing CN depending on the presence of brain metastases is presented in Table 5.16.

Table 5.16 – Distribution of mRCC patients undergoing CN depending on the presence of brain metastases

Metastasis to the brain	Number of patients	HR
Metastasis to the brain (-)	203 (89.8)	–
Metastases to the brain (+)	23 (10.2)	1.46 (0.92-2.33, p=0.110)

The presented Kaplan-Meier curves (Figure 5.17) show that the 3-year and 5-year OS rates were 61.7% [55.1-69.0%, 95% CI] and 45.3% [38.7-53.2%, 95% CI] in the absence of brain metastases, and 47.4% [30.7-73.2%, 95% CI] and 26.4% [12.7-54.6%, 95% CI] in the presence of brain metastases, respectively. The median OS was 51.7 [42.9-65.2, 95% CI] and 35.5 [18.4-86.3, 95% CI] months, respectively.

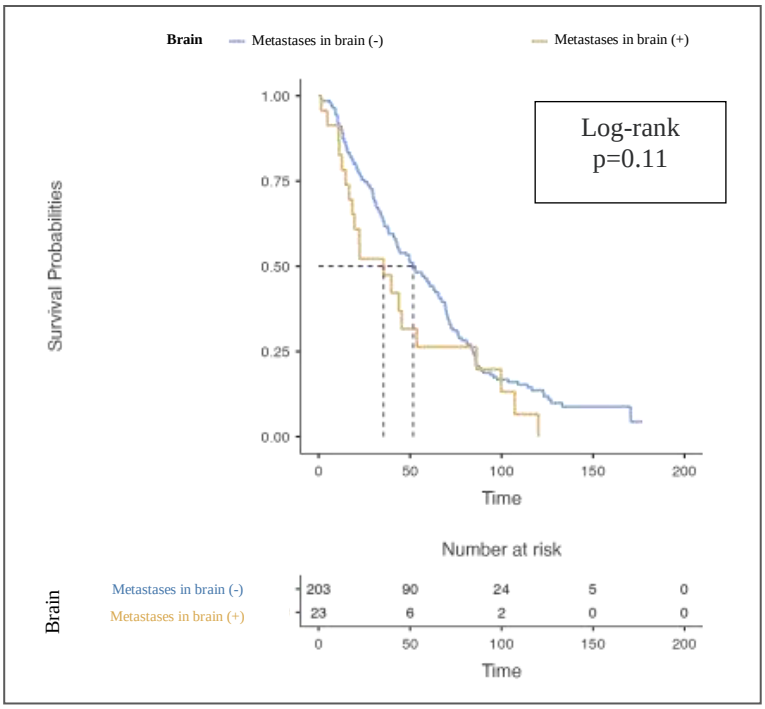


Figure 5.17 – Comparison of OS indicators of mRCC patients with absence/presence of brain metastases when performing CN (N=330)

Thus, the study did not reveal statistically significant differences in OS and median OS in mRCC patients when performing CN and absence/presence of brain metastases (p=0.11).

As presented in Table 5.17, in the single-factor analysis, histologic variant and Fuhrman grade of tumor differentiation, number of metastases, ECOG status, presence of liver metastases, and hemoglobin, alkaline phosphatase, and LDH levels were the factors influencing the OS in mRCC patients undergoing CN.

Table 5.17 – Cox proportional hazards model of the effect on OS outcomes in a group of mRCC patients, when performing CN (N=330)

Factors	Gradations	Number sick	HR (single-factor)	HR (multivariate)
Gender	men	239 (72.4)	–	–
	women	91 (27.6)	0.77 (0.59-1.00, p=0.053)	0.89 (0.67-1.18, p=0.430)
Age	18-44	19 (5.8)	–	–
	45-59	148 (44.8)	1.38 (0.76-2.50, p=0.288)	3.21 (1.56-6.59, p=0.001)
	60-74	143 (43.3)	1.21 (0.67-2.19, p=0.533)	2.57 (1.26-5.23, p=0.009)
	over 75	20 (6.1)	1.73 (0.83-3.61, p=0.143)	4.49 (1.92-10.51, p=0.001)
Localization	on the right	157 (47.6)	–	–
	on the left	164 (49.7)	0.94 (0.75-1.19, p=0.628)	1.14 (0.88-1.46, p=0.321)
	bilateral	9 (2.7)	0.84 (0.39-1.79, p=0.643)	1.48 (0.64-3.40, p=0.355)
ECOG	ECOG0	9 (2.7)	–	–
	ECOG1	105 (31.8)	1.52 (0.48-4.83, p=0.475)	0.64 (0.18-2.22, p=0.477)
	ECOG2	125 (37.9)	3.67 (1.16-11.61, p=0.027)	1.50 (0.43-5.28, p=0.524)
	ECOG3	91 (27.6)	18.83 (5.85-60.62, p<0.001)	4.70 (1.29-17.13, p=0.019)
Histological variant	clear-cell	279 (84.5)	–	–
	non- clear-cell	51 (15.5)	2.00 (1.46-2.73, p<0.001)	1.21 (0.85-1.71, p=0.290)
Degree of diffraction	Grade1	17 (5.2)	–	–
	Grade2	103 (31.2)	2.84 (1.51-5.36, p=0.001)	3.24 (1.63-6.44, p=0.001)
	Grade3	210 (63.6)	5.23 (2.83-9.70, p<0.001)	3.69 (1.90-7.18, p<0.001)

Continuation of Table 5.17

Factors	Gradations	Number sick	HR (single-factor)	HR (multivariate)
Number of metastases	solitary	16 (4.8)	–	–
	single	65 (19.7)	0.98 (0.53-1.81, p=0.955)	1.05 (0.54-2.06, p=0.882)
	multiple	249 (75.5)	3.25 (1.84-5.75, p<0.001)	2.27 (1.17-4.42, p=0.016)
Bones	bone metastases (-)	195 (59.1)	–	–
	bone metastases (+)	135 (40.9)	1.05 (0.83-1.33, p=0.681)	0.67 (0.49-0.92, p=0.012)
Lungs	lung metastases (-)	107 (32.4)	–	–
	lung metastases (+)	223 (67.6)	1.10 (0.86-1.41, p=0.442)	0.72 (0.53-0.99, p=0.043)
Liver	liver metastases (-)	285 (86.4)	–	–
	liver metastases (+)	45 (13.6)	1.89 (1.35-2.65, p<0.001)	1.40 (0.92-2.14, p=0.118)
Brain	brain metastases (-)	306 (92.7)	–	–
	brain metastases (+)	24 (7.3)	0.69 (0.42-1.13, p=0.143)	0.83 (0.45-1.53, p=0.556)
Hemoglobin	hemoglobin is normal	209 (63.3)	–	–
	anemia	121 (36.7)	2.93 (2.30-3.73, p<0.001)	2.01 (1.50-2.69, p<0.001)
Alkaline phosphatase	alkaline phosphorus is normal	213 (64.5)	–	–
	alkaline phosphorus is elevated	117 (35.5)	1.32 (1.03-1.68, p=0.027)	0.77 (0.55-1.09, p=0.145)
LDH	LDH is normal	243 (73.6)	–	–
	LDH is elevated	87 (26.4)	1.35 (1.04-1.76, p=0.023)	1.14 (0.83-1.57, p=0.418)

In multivariate analysis, age (45-59 and 60-74 years), Fuhrman tumor differentiation grade, number of metastases, ECOG status, bone metastases, and hemoglobin level were additional factors influencing OS rates in mRCC patients.

5.2 Evaluation of forecast factors and their impact on efficiency for combined cytoreductive nephrectomy and metastasectomy in patients with metastatic renal-cell cancer

In our work, we also studied mRCC patients who underwent metastasectomy synchronously with CN and considered clinical, laboratory, and pathomorphologic factors affecting survival rates.

5.2.1 Survival rates of patients depending on the from clinical characteristics in the performance of cytoreductive nephrectomy and metastasectomy

The study group included 62 patients, the mean age of the patients was 60.3±9.7 years (28 years – 76 years).

When evaluating the mRCC patients for CN and metastasectomy included in the study, it was found that males predominated in 66.1% of cases in the study (Table 5.18).

Table 5.18 – Distribution of mRCC patients undergoing CN and metastasectomy according to gender characteristics

Gender	Number of patients	HR
Men	41 (66.1)	–
Women	21 (33.9)	0.93 (0.53-1.63, p=0.803)

The results of calculating survival rates according to gender are presented in Figure 5.18.

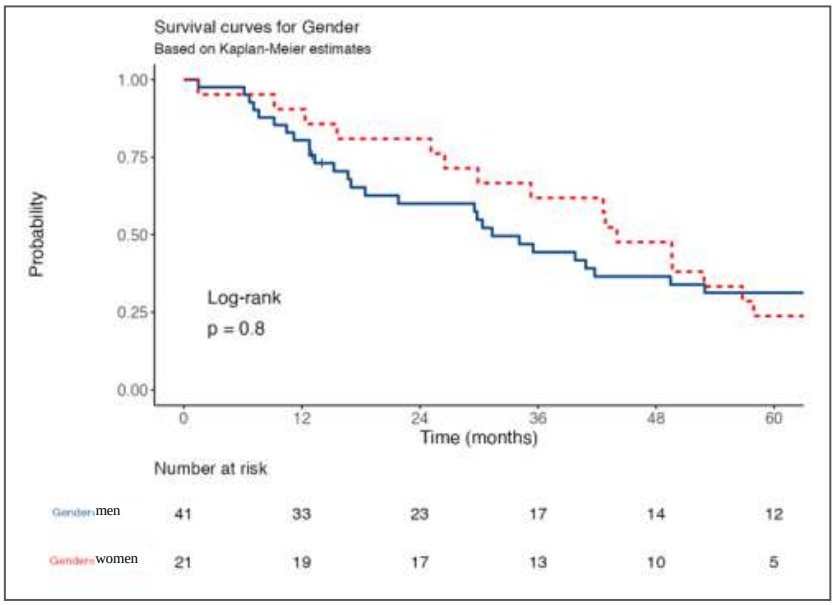


Figure 5.18 – Kaplan-Meier curves of OS indicators in mRCC patients (N=62) when performing CN and metastasectomy according to gender

Survival analysis found that the 3- and 5-year OS rates of mRCC patients undergoing CN and metastasectomy were 90.5% [78.8-100.0%, 95% CI] and 61.9% [44.3-86.6%, 95% CI], 44.4% [31.2-63.1%, 95% CI], and 31.3% [19.6-49.9%, 95% CI], respectively, depending on sex. Meanwhile, the median OS of OB was 31.3 [18.4-53, 95% CI] and 44 [29.9-65.2, 95% CI] months, respectively. Thus, the current study did not show an advantage in OS and median OS according to gender in mRCC patients when performing CN and metastasectomy (p=0.8). Thus, in the conducted study there was no advantage in the rates of OS and median OS depending on gender features in mRCC patients when performing CN and metastasectomy (p=0,8).

While evaluating the mRCC patients included in the study, it was found that the study was dominated by patients in the age range of 45-59 years at 51.6% (Table 5.19).

Table 5.19 – Distribution of mRCC patients undergoing CN and metastasectomy according to age

Age	Number of patients	HR
18-44	6 (9.7)	–
45-59	32 (51.6)	1.17 (0.45-3.08, p=0.745)
60-74	21 (33.9)	0.93 (0.34-2.54, p=0.887)
over 75	3 (4.8)	3.20 (0.76-13.51, p=0.113)

The presented Kaplan-Meier curve plot (Figure 5.19) shows that the 3-year and 5-year OS rates at ages 18-44 years were 100.0% [100.00-100.0%, 95% CI] and 20.0% [3.46-100.0%, 95% CI], 40,6% [26.72-61.8%, 95% CI] and 28.1% [16.16-48.9%, 95% CI], 55.7% [37.68-82.2%, 95% CI] and 35.4% [19.57-64.1%, 95% CI], 3-year OV was 33.3% [6.73-100.0%, 95% CI], respectively. Meanwhile, the median OS was 49.6 [49.5-NA, 95% CI], 30.6 [17-49.6, 95% CI], 52.9 [29.9-73.4, 95% CI], 9.2 [1.5-NA, 95% CI] months, respectively.

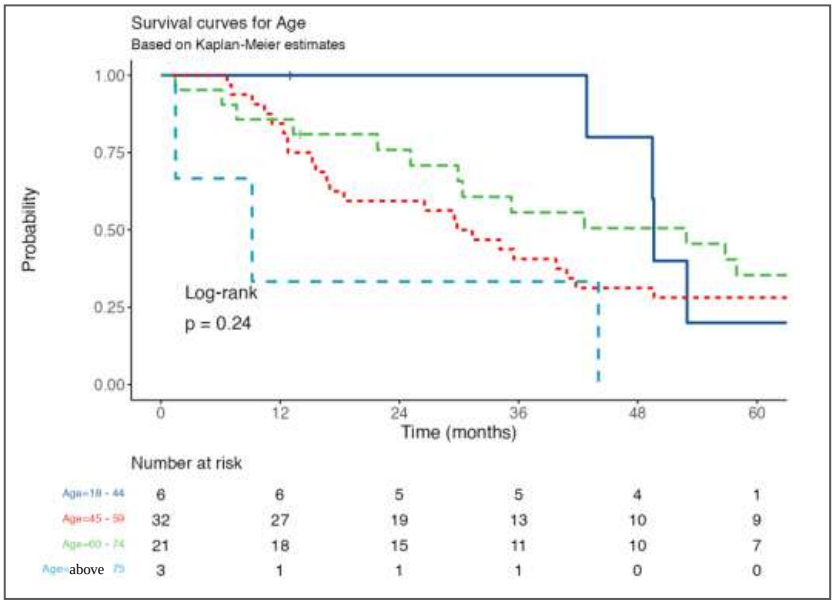


Figure 5.19 – Kaplan-Meier curves of OS indices in mRCC patients (N=62) undergoing CN and metastasectomy as a function of age

Thus, there is no advantage in the rates of OS and median OS according to age in mRCC patients when performing CN and metastasectomy (p=0.24).

The distribution of mRCC patients undergoing CN and metastasectomy depending on the localization of the primary tumor is presented in Table 5.20.

Table 5.20 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the location of the primary tumor

Localization of the primary tumor	Number of patients	HR
On the right	36 (58.1)	–
From left	25 (40.3)	0.86 (0.50-1.48, p=0.583)
Bilateral	1 (1.6)	1.11 (0.15-8.19, p=0.920)

Survival analysis found that the 3-year and 5-year OS rates depending on the location of the patients' primary kidney tumor were 47.22% [33.4-66,70%, 95% CI] and 25.00% [14.2-44.02%, 95% CI], on the left – 53.05% [36.1-77.86%, 95% CI] and 35.37% [20.3-61.57%, 95% CI], with both kidneys affected – 3-year OS rates – 100.00% [100.0-100.00%, 95% CI], respectively. Meanwhile, the median OS was 35.4 [29.5-49.5, 95% CI], 49.6 [18.4-75.5, 95% CI], and 42.9 [NA-NA, 95% CI] months, respectively (Figure 5.20).

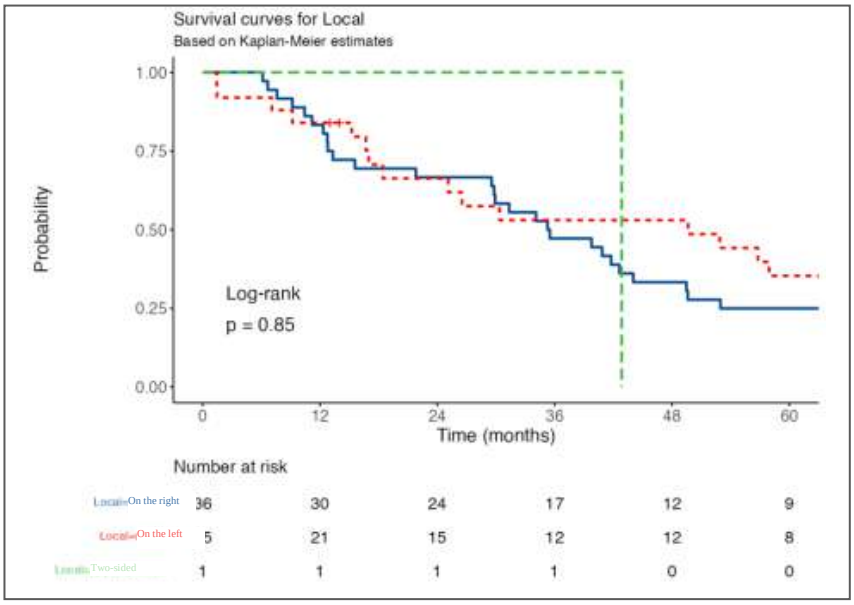


Figure 5.20 – Kaplan-Meier curves of OS parameters in mRCC patients (N=62) when performing CN and metastasectomy depending on the side of the primary tumor involved

Thus, the conducted study revealed no statistically significant differences in the rates of OS and median OS depending on the localization of the primary tumor in mRCC patients when performing CN and metastasectomy (p=0.85).

When evaluating the mRCC patients for CN and metastasectomy included in the study according to ECOG status, Table 5.21 shows that patients with ECOG 2-3 somatic status predominated in 70.9% of cases.

Table 5.21 – Distribution of mRCC patients undergoing CN and metastasectomy depending on ECOG status

ECOG status	Number of patients	HR
ECOG0	3 (4.8)	–
ECOG1	15 (24.2)	0.81 (0.18-3.69, p=0.782)
ECOG2	25 (40.3)	2.82 (0.64-12.37, p=0.169)
ECOG3	19 (30.6)	14.01 (2.95-66.54, p=0.001)

The presented Kaplan-Meier curves (Figure 5.21) demonstrated that the 3-year and 5-year OS rates of patients with ECOG0 status were 100.00% [100.0-100.0%, 95% CI] and 50.00% [12.5-100.0%, 95% CI], respectively, With ECOG1, 92.86% [80.3-100.0%, 95% CI] and 64.29% [43.5-95.0%, 95% CI], respectively. At ECOG2, 52.00% [35.7-75.8%, 95% CI] and 28.00% [14.9-52.5%, 95% CI], respectively. At ECOG3, the 3-year OV was 10.53% [2.8-39.0%, 95% CI], respectively. Meanwhile, the median OS was – 78.3 [56.8-NA, 95% CI], 74.9 [57.9-NA, 95% CI], 40.9 [30.4-65.2, 95% CI], and 12.3 [9.2-29.5, 95% CI] months at ECOG 0, 1, 2, 3, respectively.

Thus, the study revealed statistically significant differences in the rates of OS and median OS in mRCC patients undergoing CN and metastasectomy depending on ECOG status (p<0.0001).

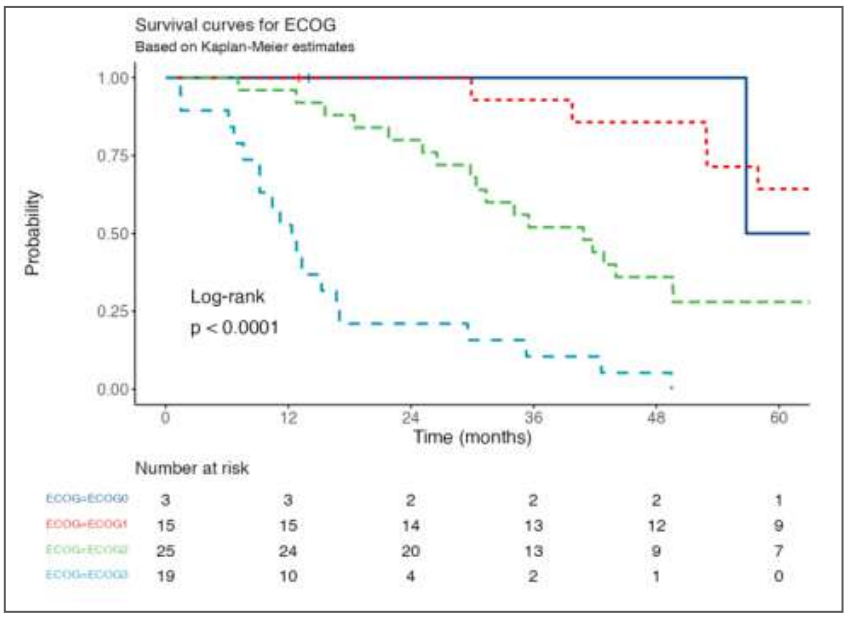


Figure 5.21 – Kaplan-Meier curves of OS rates in mRCC patients undergoing CN and metastasectomy depending on ECOG status (N=62)

Despite the fact that we consider separately the factors included in the IMDC prognostic model, we evaluated the survival rates of patients undergoing CN and metastasectomy in 3 prognostic groups in the total cohort of patients. Table 5.22 shows that of the 62 patients who underwent CN and metastasectomy, 4 (6.5%) were in the favorable prognosis group, 19 (30.6%) in the intermediate prognosis group, and 39 (62.9%) in the poor prognosis group. Thus, more than 90% of mRCC patients were from the intermediate and poor prognosis groups according to IMDC.

Table 5.22 – Distribution of mRCC patients undergoing CN and metastasectomy according to IMDC prognosis

IMDC Forecast	Number of patients	HR
Favorable	4 (6.5)	–
Intermediate	19 (30.6)	5.03 (1.13-22.48, p=0.034)
Poor	39 (62.9)	7.62 (1.80-32.28, p=0.006)

The presented Kaplan-Meier curve diagram (Figure 5.22) shows that OS rates are directly related to IMDC prognosis. Thus, in the favorable prognosis group, the 3- and 5-year OS of patients were 100.00% [100.0-100.0%, 95% CI] and 100.00% [100.0-100.0%, 95% CI], and in the intermediate prognosis group, 64.71% [45.5-91.9%, 95% CI] and 23.53% [10.0-55.4%, 95% CI]. And the OS rates in the Poor prognosis group were 38.46% [25.9-57.2%, 95% CI] and 23.08% [13.0-40.9%, 95% CI], respectively. Meanwhile, the median OS also differed and was 99.8 [85.9-NA, 95% CI], 42.9 [35.5-65.2, 95% CI], and 25.1 [15.2-49.5, 95% CI] months, respectively.

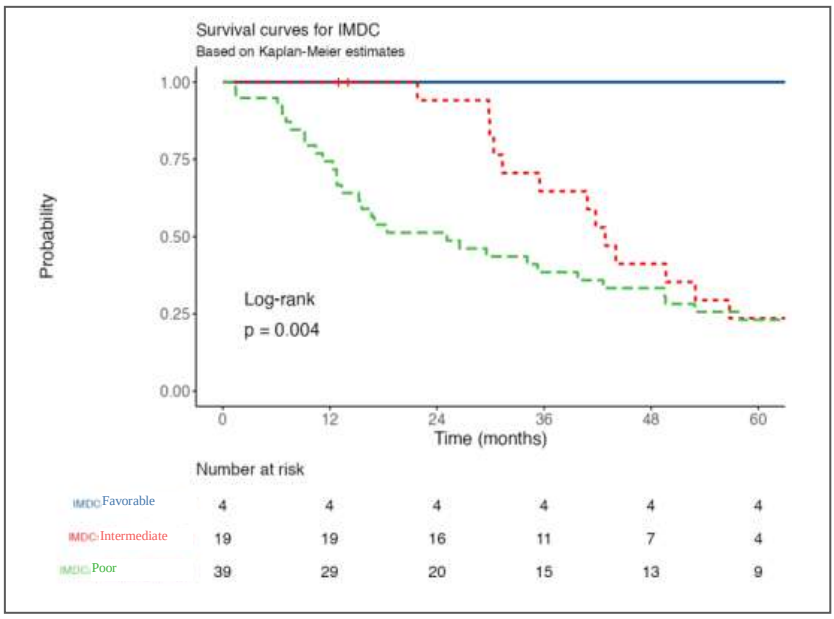


Figure 5.22 – Kaplan-Meier curves of OS indicators in mRCC patients when performing CN and metastasectomy.
depending on IMDC prognosis (N=62)

Thus, the study revealed statistically significant differences in OS and median OS depending on IMDC prognosis in mRCC patients undergoing CN and metastasectomy (p=0.004).

5.2.2 Impact on patient survival rates metastatic renal cell cancer when performing cytoreductive nephrectomy and metastasectomy morphologic characteristics of the tumor

When evaluating the mRCC patients included in the study depending on the histologic variant, 56 (90.3%) patients were verified as having clear cell carcinoma in the majority of cases. Non-small cell variants accounted for 6 (9.7%) cases (Table 5.23).

Table 5.23 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the histological subtype of the primary tumor

Histologic variant	Number of patients	HR
Clear-cell	56 (90.3)	–
Non- clear-cell	6 (9.7)	1.80 (0.75-4.32, p=0.191)

The presented Kaplan-Meier curve plot (Figure 5.23) shows that the 3-year and 5-year OS rates for luminal carcinoma were 52.41% [41-67.5%, 95% CI] and 31.82% [22-47.1%, 95% CI], and 33.33% [11-100.0%, 95% CI] and 0% for non-small cell carcinoma, respectively. The median OS was 40.9 [29.8-56.8, 95% CI] and 32.8 [29.5-NA, 95% CI] months, respectively.

Thus, the study did not reveal statistically significant differences in OS and median OS rates depending on the histological subtype of tumor in mRCC patients when performing CN and metastasectomy (p=0.18).

When evaluating the patients included in the study depending on the degree of differentiation according to Fuhrman were distributed as follows. Table 5.24 shows that the number of patients at G1 was 2 (3.2%), at G2 – 19 (30.6%) and G3 – in 41 (66.1%) patients, respectively. Thus, more than 60% of patients had low-differentiated tumors.

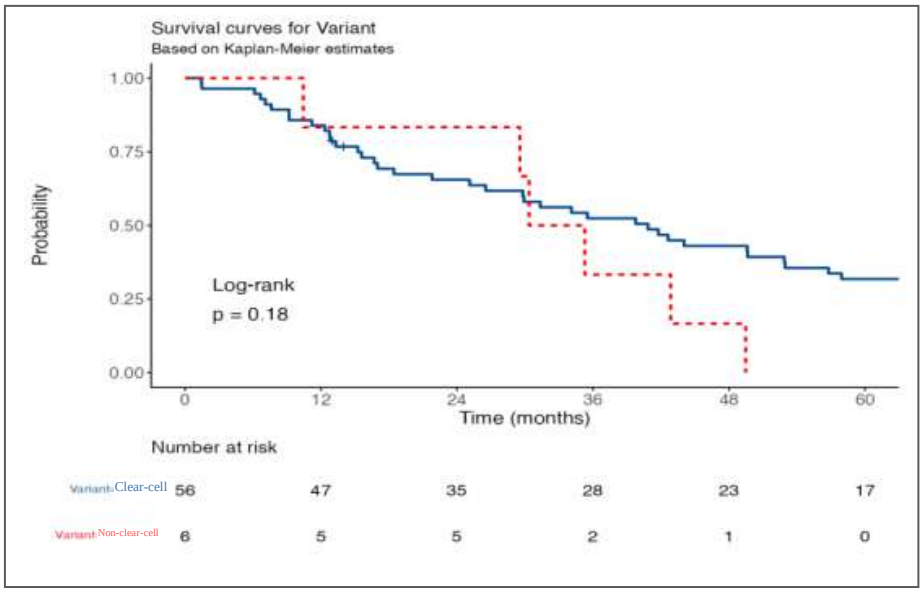


Figure 5.23 – Kaplan-Meier curves of OS indices of mRCC patients (N=62) depending on the histological variant of the tumor when performing CN and metastasectomy.

Table 5.24 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the degree of tumor differentiation according to Fuhrman

Degree of tumor differentiation	Number of patients	HR
Grade 1	2 (3.2)	–
Grade 2	19 (30.6)	64418879.94 (0.00-Inf, p=0.996)

The presented Kaplan-Meier curves (Figure 5.24), it can be seen that the 3-year and 5-year OS depending on tumor differentiation according to Fuhrman were 100.0% [100.0-100.0%, 95% CI] and 100.0% [100.0-100.0%, 95% CI], 65.4% [46.3-92.3%, 95% CI] and 35.7% [18.8-67.6%, 95% CI], 41.5% [28.8-59.7%, 95% CI] and 22.0% [12.3-39.1%, 95% CI], respectively. The median OS in highly differentiated tumor was not reached, and in moderately and low differentiated tumor was 53 [31.3-73.4, 95% CI] and 29.8 [17-42.6, 95% CI] months, respectively, Thus, our study revealed statistically significant differences in the OS and median OS of mRCC patients when performing CN and metastasectomy depending on the degree of tumor differentiation according to Fuhrman (p=0.0019).

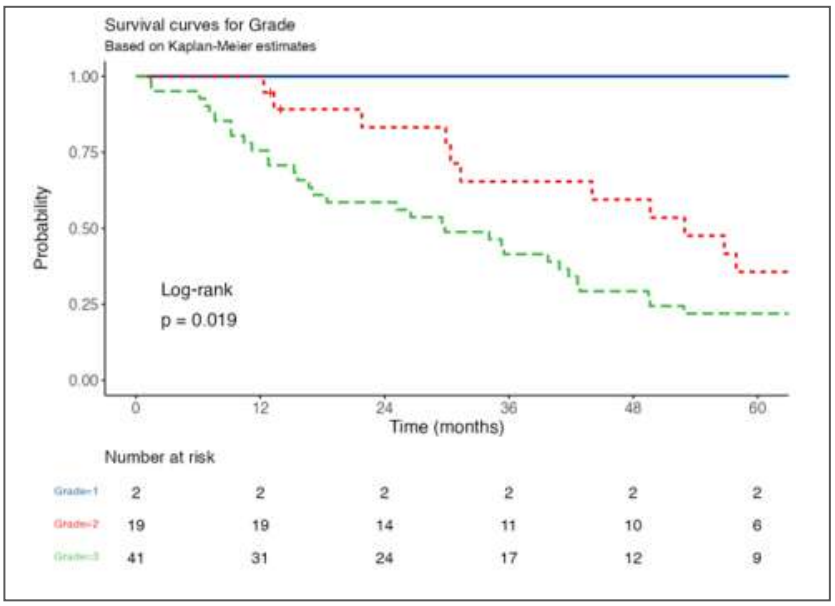


Figure 5.24 – Kaplan-Meier curves of OS indicators of mRCC patients when performing CN and metastasectomy (N=62) depending on tumor differentiation according to Fuhrman

Solitary metastases were detected in 4 (6.5%) patients, single metastases in 16 (25.8%) and multiple metastases in 42 (67.7%) patients (Table 5.25).

Table 5.25 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the number of metastases

Number of metastases	Number of patients	HR
Solitary	4 (6.5)	–
Single	16 (25.8)	0.76 (0.24-2.40, p=0.638)
Multiple	42 (67.7)	5.93 (1.81-19.49, p=0.003)

As can be seen from Figure 5.25, survival rates directly depend on the number of metastases. Thus, in patients with solitary, single, and multiple metastases, the 3- and 5-year OS rates were 75.0% [42,59-100.0%, 95% CI] and 75.0% [42.59-100.0%, 95% CI], 100.0% [100.00-100.0%, 95% CI], 93.8% [82.61-100.0%, 95% CI] and 62.5% [42.76-91.4%, 95% CI], 30.7% [19.26-49.0%, 95% CI] and 10.2% [4.06-25.9%, 95% CI], respectively. Meanwhile, the median OS also differed and was

80.1 [15.2-NA, 95% CI], 74.4 [52.9-NA, 95% CI], and 29.5 [17-35.5, 95% CI] months, respectively.

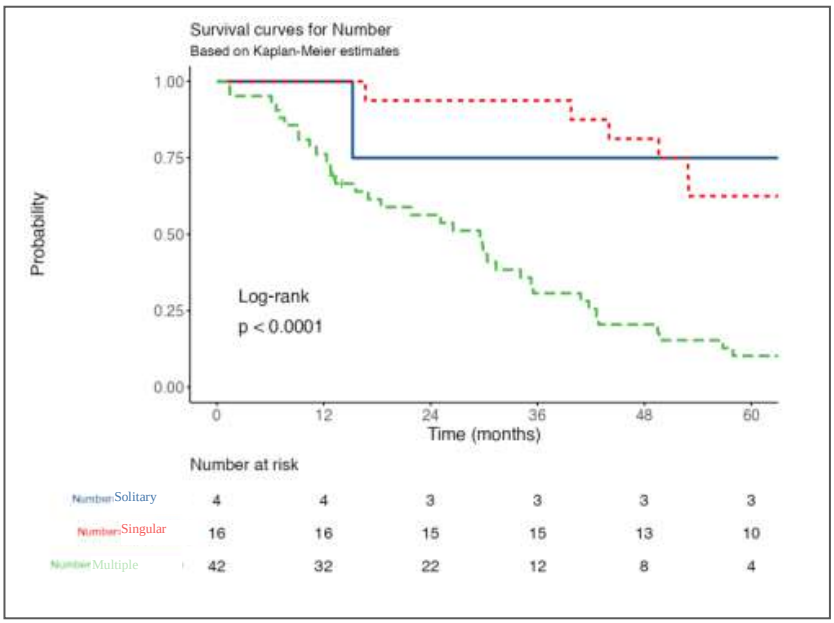


Figure 5.25 – Kaplan-Meier curves of OS indices of mRCC patients (N=62) when performing CN and metastasectomy depending on the amount of metastasis

Thus, the conducted study revealed statistically significant differences in OB and median OS in mRCC patients when performing CN and metastasectomy depending on the number of metastases (p<0.0001).

5.2.3 Impact of laboratory data on survival rates of patients with metastatic renal cell cancer when performing cytoreductive nephrectomy and metastasectomy

When evaluating the patients included in the study depending on the hemoglobin level were distributed as follows. Thus, normal hemoglobin level was noted in 41 (66.1%) patients and anemia was noted in 21 (33.9%) patients. Thus, one-third of the mRCC patients in our study had anemia, as shown in Table 5.26.

Table 5.26 – Distribution of mRCC patients undergoing CN and metastasectomy depending on hemoglobin level

Hemoglobin level	Number of patients	HR
Hemoglobin's normal	41 (66.1)	–
Anemia	21 (33.9)	2.31 (1.33-4.01, p=0.003)

The presented Kaplan-Meier curves (Figure 5.26) show that the 3-year and 5-year OS rates for normal hemoglobin were 64.4% [51.0-81.3%, 95% CI] and 36.0% [23.7-54.8%, 95% CI], respectively. In anemia, these rates decreased significantly to 23.8% [11.1-51.2%, 95% CI] and 14.3% [5.0-40.7%, 95% CI], respectively. The median OS also differed according to hemoglobin level and was 49.5 [39.8-70.3, 95% CI] and 13.3 [9.2-42.6, 95% CI] months, respectively.

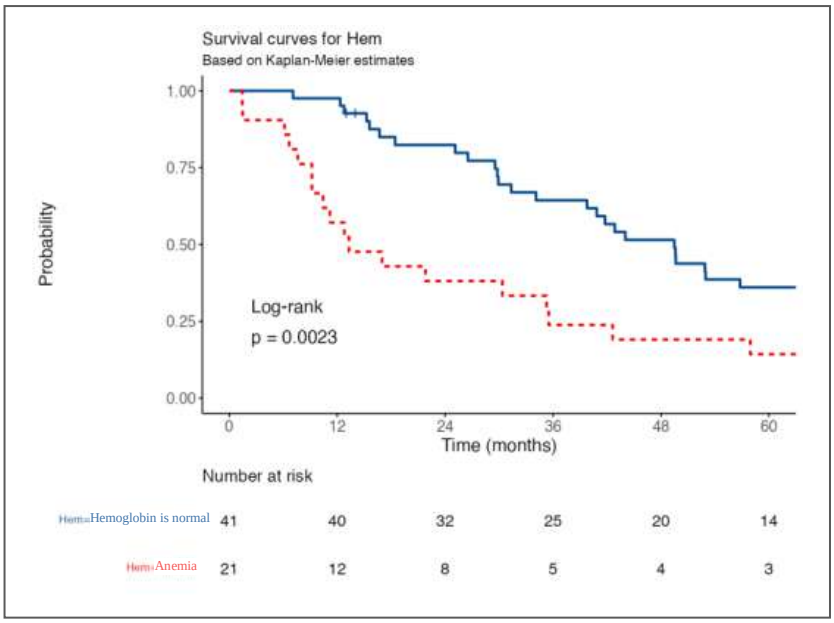


Figure 5.26 – Comparison of OS of patients with mRCC (N=62) under CN and metastasectomy depending on hemoglobin level

Thus, the conducted study revealed statistically significant differences in OS and median OS depending on hemoglobin level in mRCC patients when performing CN and metastasectomy (p=0.0023).

When evaluating the patients included in the study depending on the level of alkaline phosphorus were distributed as follows. Thus, as can be seen from Table 5.27, a normal level of alkaline phosphorus was detected in 38 (61.3%) patients, and elevation of this index was noted in 24 (38.7%) patients. Thus, 2/3 of patients with mRCC had normal alkaline phosphate levels.

Table 5.27 – Distribution of mRCC patients under CN and metastasectomy depending on alkaline phosphate levels

Alkaline phosphatase level	Number of patients	HR
alkaline phosphorus is normal	38 (61.3)	–
alkaline phosphorus is elevated	24 (38.7)	1.24 (0.72-2.11, p=0.441)

Figure 5.27 shows that the 3-year and 5-year OS rates with normal alkaline phosphorus were 52.63% [38.9-71.2%, 95% CI] and 28.95% [17.6-47.6%, 95% CI], respectively.

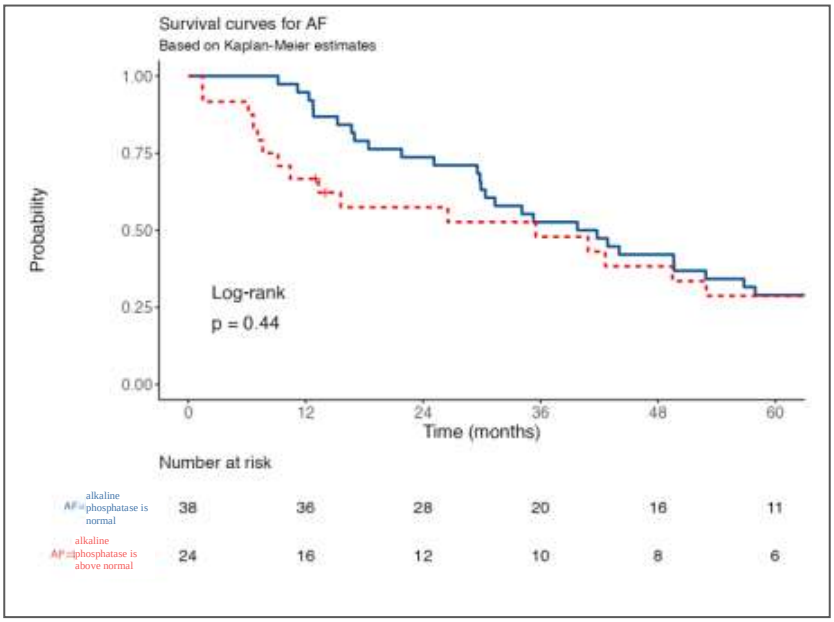


Figure 5.27 – Comparison of OS indicators of patients with mRCC (N=62) during CN and metastasectomy depending on alkaline phosphate levels

When alkaline phosphorus was elevated, these rates decreased to 47.86% [31.1-73.8%, 95% CI] and 28.72% [14.8-55.9%, 95% CI], respectively. Meanwhile, the median OS was 40.8 [29.9-57.9, 95% CI] and 35.5 [13.3-67.4, 95% CI] months, respectively. Thus, the study did not reveal statistically significant differences in OS and median OS depending on the level of alkaline phosphate in patients with mRCC at CN and metastasectomy (p=0.44).

When evaluating the patients included in the study depending on the LDH level were distributed as follows. Thus, a normal LDH level was noted in 42 (67.7%) patients, and an elevation of this indicator was found in 20 (32.3%) patients, as shown in Table 5.28.

Table 5.28 – Distribution of mRCC patients undergoing CN and metastasectomy depending on LDH level

LDH	Number of patients	HR
LDH is normal	42 (67.7)	–
LDH is elevated	20 (32.3)	1.06 (0.60-1.86, p=0.836)

The presented Kaplan-Meier curves (Figure 5.28) show that the 3-year and 5-year OS rates for LDH in normal patients were 49.1% [35.92-67.0%, 95% CI] and 31.9% [20.38-49.9%, 95% CI], respectively. When LDH levels were elevated, these rates worsened to 53.6% [35.31-81.3%, 95% CI] and 21.4% [9.01-50.9%, 95% CI], respectively. Meanwhile, median OS was 35.5 [29.8-57.9, 95% CI] and 39.8 [16.7-69, 95% CI] months, respectively.

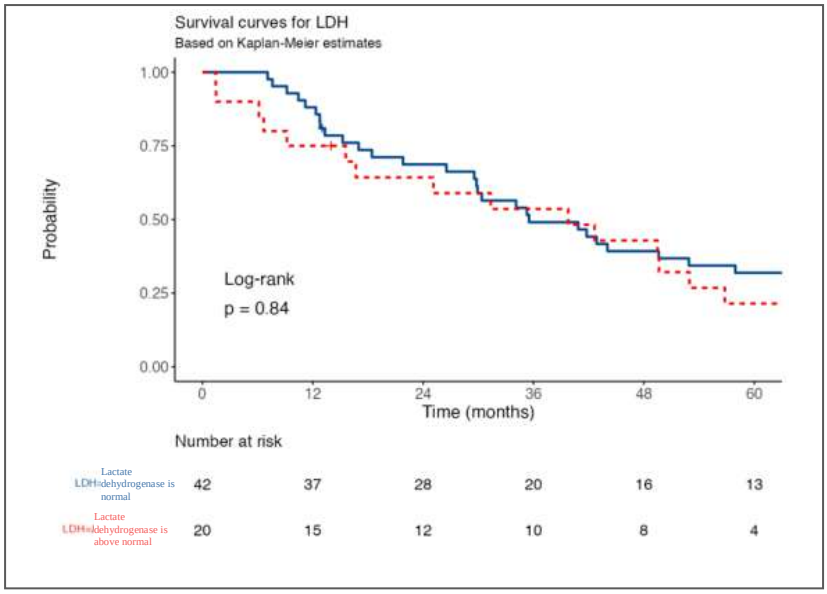


Figure 5.28 – Comparison of OS indicators of patients with mRCC (N=62) during CN and metastasectomy depending on LDH levels

Thus, the conducted study showed no statistically significant differences in OS and median OS depending on LDH level in mRCC patients when performing CN and metastasectomy (p=0.84).

5.2.4 Influence of metastases localization on the indices of survival rates of patients with metastatic renal-cell carcinoma when performing cytoreductive nephrectomy and metastasectomy

The distribution of mRCC patients undergoing CN and metastasectomy depending on the presence of bone metastases is presented in Table 5.29.

Table 5.29 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the presence of bone metastases

Bone metastasis	Number of patients	HR
Bone metastasis (-)	22 (35.5)	–
Bone metastases (+)	40 (64.5)	1.45 (0.84-2.50, p=0.186)

Survival analysis found that the 3-year and 5-year OS rates in the absence of bone metastases were 59.1% [41.7-83.7%, 95% CI] and 36.4% [20.9-63.2%, 95% CI], and in the presence of bone metastases were 45.6% [32.2-64.5%, 95% CI] and 24.1% [13.7-42.5%, 95% CI], respectively. The median OS was 46.2 [30.4-73.4, 95% CI] and 35.3 [21.8-49.6, 95% CI] months, respectively (Figure 5.29).

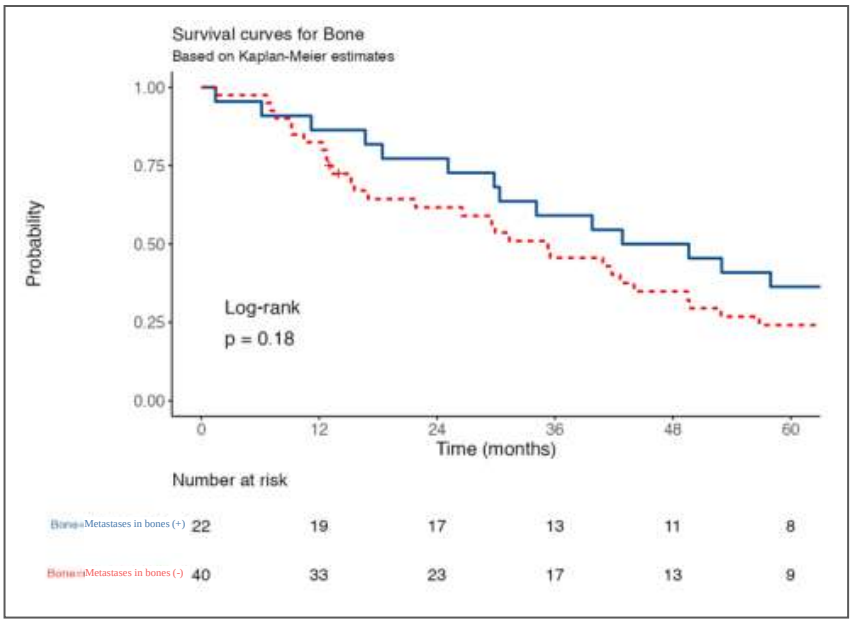


Figure 5.29 – Comparison of OS indicators of mRCC patients with absence/presence of bone metastases when performing CN and metastasectomy (N=62)

Thus, the study did not reveal statistically significant differences in OS and median OS in mRCC patients undergoing CN and metastasectomy in the absence/absence of bone metastases (p=0.18).

The distribution of mRCC patients undergoing CN and metastasectomy depending on the presence of lung metastases is presented in Table 5.30.

Table 5.30 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the presence of lung metastases

Metastasis to the lungs	Number of patients	HR
Lung metastasis (-)	28 (45.2)	–
Lung metastasis (+)	34 (54.8)	1.15 (0.67-1.96, p=0.609)

The presented Kaplan-Meier curves (Figure 5.30) show that the 3-year and 5-year OS rates in the absence of lung metastases were 53.57% [37.95-75.6%, 95% CI] and 28.57% [15.91-51.3%, 95% CI], and in the presence of lung metastases were 47.79% [33.29-68.6%, 95% CI] and 28.68% [16.56-49.7%, 95% CI], respectively. The median OS was 40.3 [18.4-75.5, 95% CI] and 35.5 [29.8-57.9, 95% CI] months, respectively.

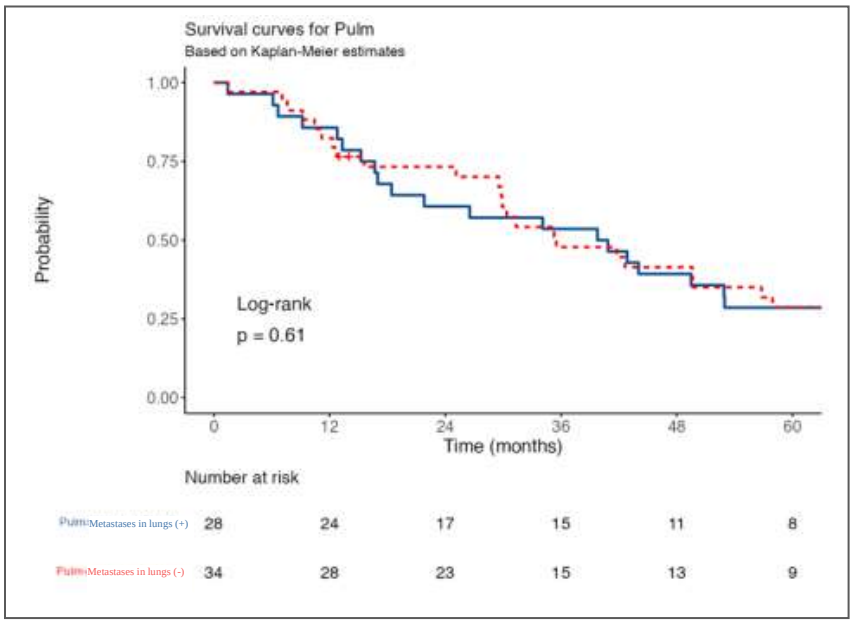


Figure 5.30 – Comparison of OS indicators of mRCC patients with absence/presence of lung metastases when performing CN and metastasectomy (N=62)

Thus, the study revealed no statistically significant differences in the rates of OS and median OS in mRCC patients undergoing CN and metastasectomy in the absence/presence of lung metastases (p=0.61).

The distribution of mRCC patients undergoing CN and metastasectomy depending on the presence of liver metastases is presented in Table 5.31.

Table 5.31 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the presence of liver metastases

Metastasis to the liver	Number of patients	HR
Metastasis to the liver (-)	56 (90.3)	–
Metastasis to the liver (+)	6 (9.7)	1.78 (0.75-4.22, p=0.192)

Figure 5.31 shows that the 3-year and 5-year OS rates were 50.43% [38.7-65.68%, 95% CI] and 29.89% [19.8-45.01%, 95% CI] in the absence of liver metastases, and 50.00% [22.5-100.00%, 95% CI] and 16.67% [2.8-99.74%, 95% CI] in the presence of liver metastases, respectively. Meanwhile, the median OS was 39.8 [29.8-52.9, 95% CI] and 28.6 [6.1-NA, 95% CI] months, respectively.

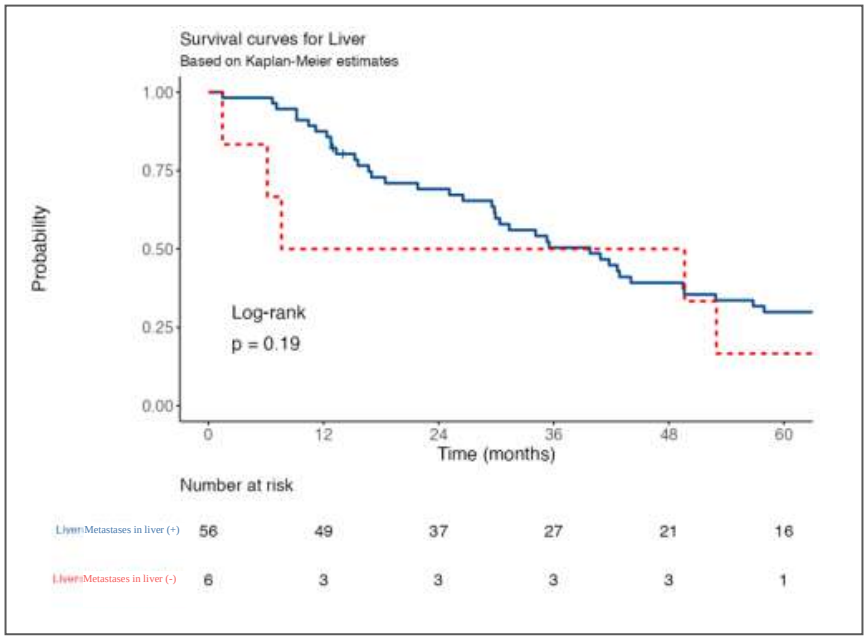


Figure 5.31 – Comparison of OS indicators of mRCC patients with absence/presence of liver metastases when performing CN and metastasectomy (N=62)

The distribution of mRCC patients undergoing CN and metastasectomy depending on the presence of brain metastases is presented in Table 5.32.

Table 5.32 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the presence of brain metastases

Metastasis to the brain	Number of patients	HR
Metastasis to the brain (-)	54 (87.1)	–
Metastases to the brain (+)	8 (12.9)	0.60 (0.26-1.35, p=0.213)

The presented Kaplan-Meier curves (Figure 5.32) show that the 3-year and 5-year OS rates were 50.59% [38.7-66.146%, 95% CI] and 27.24% [17.4-42.532%, 95% CI] in the absence of brain metastases, and 50.00% [25.0-99.980%, 95% CI] and 37.50% [15.3-91.738%, 95% CI] in the presence of brain metastases, respectively. Meanwhile, the median OS was 40.9 [29.8-52.9, 95% CI] and 37.6 [18.4-NA, 95% CI] months, respectively.

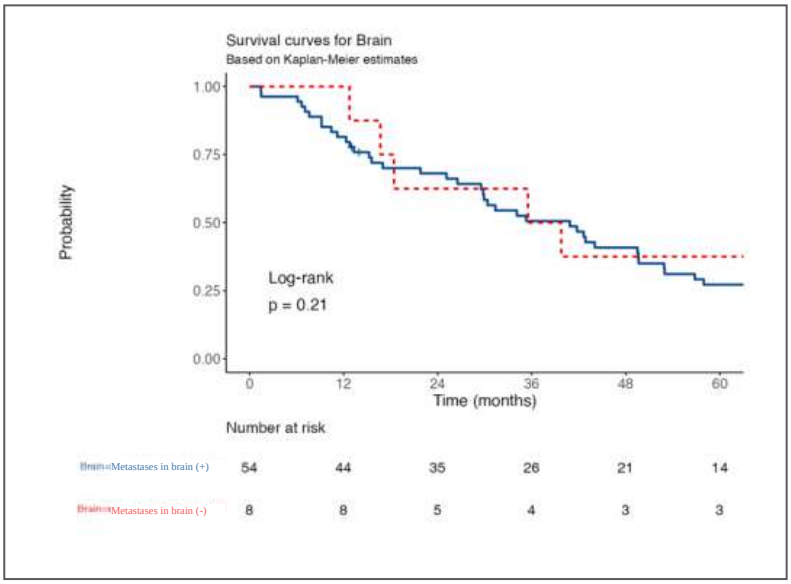


Figure 5.32 – Comparison of OS indicators of mRCC patients with absence/presence of brain metastases when performing CN and metastasectomy (N=62)

Thus, the study revealed no statistically significant differences in the rates of OS and median OS in mRCC patients undergoing CN and metastasectomy in the absence/absence of brain metastases (p=0.21).

For this subgroup of mRCC patients who underwent CN and metastasectomy, we performed single- and multivariate Cox analysis. The data are presented in Table 5.33.

Table 5.33 – Cox proportional hazards model of the effect on OS rates in the group of mRCC patients who underwent a combination of cytoreductive nephrectomy and metastasectomy (N=62)

Factors	Gradations	Number sick	HR (single-factor)	HR (multivariate)
Gender	men	41 (66.1)	–	–
	women	21 (33.9)	0.93 (0.53-1.63, p=0.803)	0.42 (0.14-1.29, p=0.130)
Age	18-44	6 (9.7)	–	–
	45-59	32 (51.6)	1.17 (0.45-3.08, p=0.745)	1.29 (0.23-7.35, p=0.772)
	60-74	21 (33.9)	0.93 (0.34-2.54, p=0.887)	1.05 (0.20-5.55, p=0.956)
	over 75	3 (4.8)	3.20 (0.76-13.51, p=0.113)	15.53 (1.46-165.34, p=0.023)
Localization	on the right	36 (58.1)	–	–
	on the left	25 (40.3)	0.86 (0.50-1.48, p=0.583)	1.47 (0.66-3.28, p=0.345)
	bilateral	1 (1.6)	1.11 (0.15-8.19, p=0.920)	3.83 (0.18-82.11, p=0.391)
ECOG	ECOG0	3 (4.8)	–	–
	ECOG1	15 (24.2)	0.81 (0.18-3.69, p=0.782)	0.61 (0.07-5.41, p=0.657)
ECOG	ECOG2	25 (40.3)	2.82 (0.64-12.37, p=0.169)	0.98 (0.12-7.93, p=0.982)
	ECOG3	19 (30.6)	14.01 (2.95-66.54, p=0.001)	24.12 (1.69-343.55, p=0.019)
Histological variant	clear-cell	56 (90.3)	–	–
	non- clear-cell	6 (9.7)	1.80 (0.75-4.32, p=0.191)	0.21 (0.05-0.96, p=0.044)
Degree differentiations	1	2 (3.2)	–	–

Continuation of Table 5.33

Factors	Gradations	Number sick	HR (single-factor)	HR (multivariate)
Degree differentiations	2	19 (30.6)	64418879.94 (0.00-Inf, p=0.996)	183244981.30 (0.00-Inf, p=0.997)
	3	41 (66.1)	98393484.29 (0.00-Inf, p=0.996)	235561778.90 (0.00-Inf, p=0.997)
Number metastases	solitary	4 (6.5)	–	–
	single	16 (25.8)	0.76 (0.24-2.40, p=0.638)	1.30 (0.24-7.13, p=0.765)
	multiple	42 (67.7)	5.93 (1.81-19.49, p=0.003)	9.54 (1.54-58.95, p=0.015)
Bones	bone metastases (-)	22 (35.5)	–	–
	bone metastases (+)	40 (64.5)	1.45 (0.84-2.50, p=0.186)	0.35 (0.13-0.90, p=0.030)
Lungs	metastases to the lungs (-)	28 (45.2)	–	–
	lung metastasis (+)	34 (54.8)	1.15 (0.67-1.96, p=0.609)	1.27 (0.56-2.90, p=0.563)
Liver	liver metastases (-)	56 (90.3)	–	–
	liver metastases (+)	6 (9.7)	1.78 (0.75-4.22, p=0.192)	2.68 (0.70-10.25, p=0.149)
Brain	brain metastases (-)	54 (87.1)	–	–
	brain metastases (+)	8 (12.9)	0.60 (0.26-1.35, p=0.213)	1.19 (0.32-4.41, p=0.794)
Hemoglobin	hemoglobin is normal	41 (66.1)	–	–
	anemia	21 (33.9)	2.31 (1.33-4.01, p=0.003)	0.56 (0.19-1.63, p=0.285)
Alkaline phosphatase	alkaline phosphorus is normal	38 (61.3)	–	–

Continuation of Table 5.33

Factors	Gradations	Number sick	HR (single-factor)	HR (multivariate)
Alkaline phosphatase	alkaline phosphorus is elevated	24 (38.7)	1.24 (0.72-2.11, p=0.441)	0.99 (0.38-2.54, p=0.976)
LDH	LDH is normal	42 (67.7)	–	–
	LDH is elevated	20 (32.3)	1.06 (0.60-1.86, p=0.836)	0.67 (0.25-1.83, p=0.437)

In the single-factor analysis, ECOG status, number of metastases, and hemoglobin level were factors influencing the OS rates in mRCC patients. In a multivariate analysis, age (older than 75 years), histologic type, ECOG status, number of metastases, and bone metastases were additional prognostic factors affecting OS rates in mRCC patients who underwent cytoreductive nephrectomy and metastasectomy.

5.3 Evaluation of forecast factors and their impact on efficiency in the absence of cytoreductive nephrectomy in patients with metastatic renal cell cancer

We retrospectively analyzed the database of 73 patients with mRCC who did not undergo CN and received only systemic drug therapy. Cytoreductive surgery was not performed due to low ECOG status due to complications of the underlying disease. These were mainly manifestations of visceral crisis in the form of anemia, thrombosis, etc.

5.3.1 Survival rates of patients depending on the from clinical characteristics in the absence of cytoreductive nephrectomy performance

The presented Kaplan-Meier curves (Figure 5.33) show that the 3- and 5-year OS of patients in the absence of CN were 20.5±1.4% and 8.2±1.4% months, respectively. The median OS was 11 months.

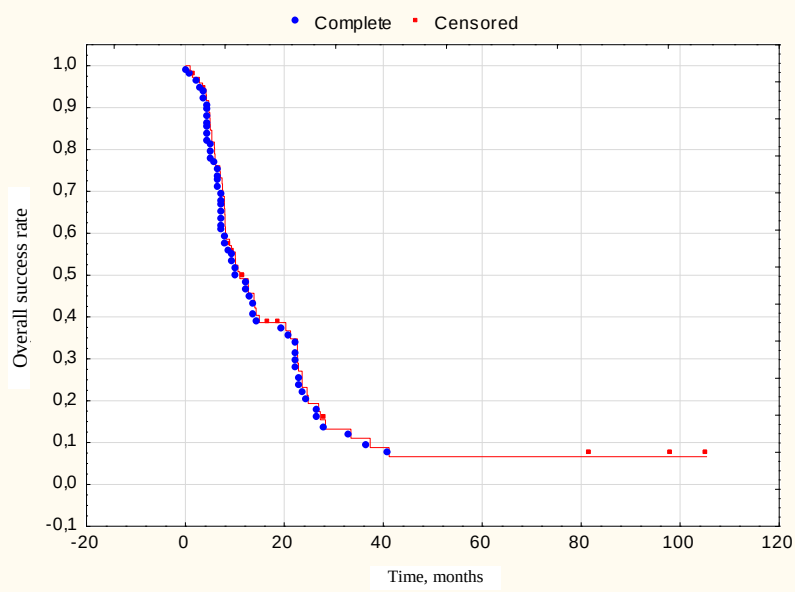


Figure 5.33 – OS rates of mRCC patients (N=73) in the absence of CN. The mean age of the patients included in the study was 60.4±9.2 years (36 years – 82 years)

While evaluating the mRCC patients included in the study, it was found that the study was dominated by patients in the age range of 45-59 years at 46.6% (Table 5.34).

Table 5.34 – Distribution of mRCC patients without CN according to age

Age	Number of patients	HR
18-44	2 (2.7)	–
45-59	34 (46.6)	1.45 (0.19-10.80, p=0.716)
60-74	33 (45.2)	1.60 (0.22-11.84, p=0.647)
Over 75	4 (5.5)	1.84 (0.20-16.67, p=0.588)

The presented Kaplan-Meier curve plot (Figure 5.34) shows that the 1-year OS rates at age 18-44 years were 50.0% [12.5-100.0%, 95% CI%, and the 3-year and 5-year OS rates at age 45-59 years were 18.4% [8.4-40.0%, 95% CI] and 13.8% [5.3-36.1%, 95% CI], respectively. And in patients at age 60-74 years, the rates of 3-year and 5-year OS were 4.7% [0.7-31.1%, 95% CI] and 0%, respectively. In patients over 75 years of age, the rates of 1-year OS were 50.0% [18.8-100.0%, 95% CI], With a median OS of 9.3 [9.3-NA, 95% CI], 12.7 [7.5-22.7, 95% CI], 11 [8-23.6, 95% CI], and 10 [5-NA, 95% CI] months, respectively. Thus, in the current study, there was no advantage in OS and median OS according to age in mRCC patients in the absence of performing CN (p=0.93).

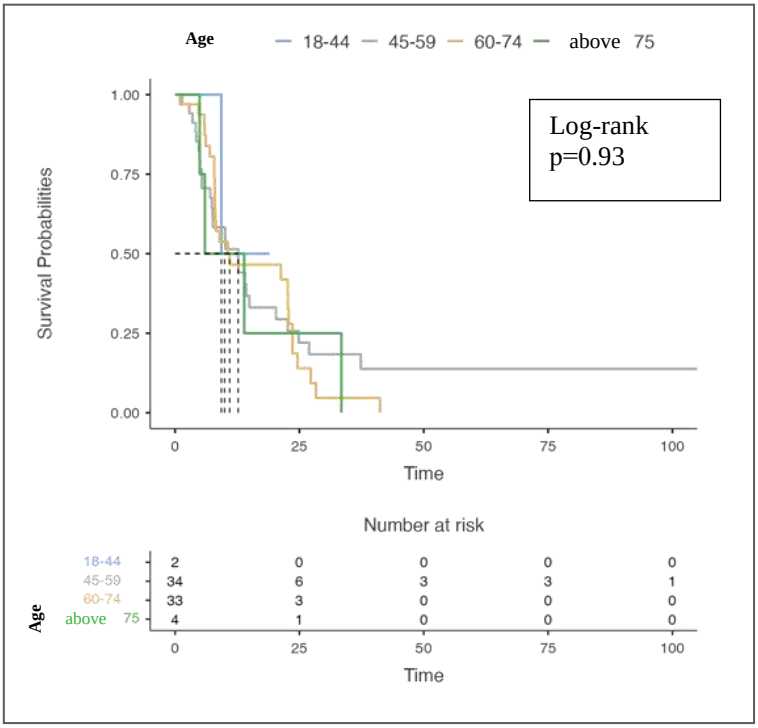


Figure 5.34 – Kaplan-Meier curves of OS indices in mRCC patients (N=73) in the absence of CN performance as a function of age

When evaluating the mRCC patients in the absence of performing CN included in the study, it was found that males predominated in 75.3% of cases in the study (Table 5.35).

Table 5.35 – Distribution of mRCC patients undergoing CN and metastasectomy according to gender characteristics

Gender	Number of patients	HR
Male	55 (75.3)	–
Female	18 (24.7)	1.31 (0.71-2.40, p=0.391)

The results of calculating survival rates according to gender are presented in Figure 5.35.

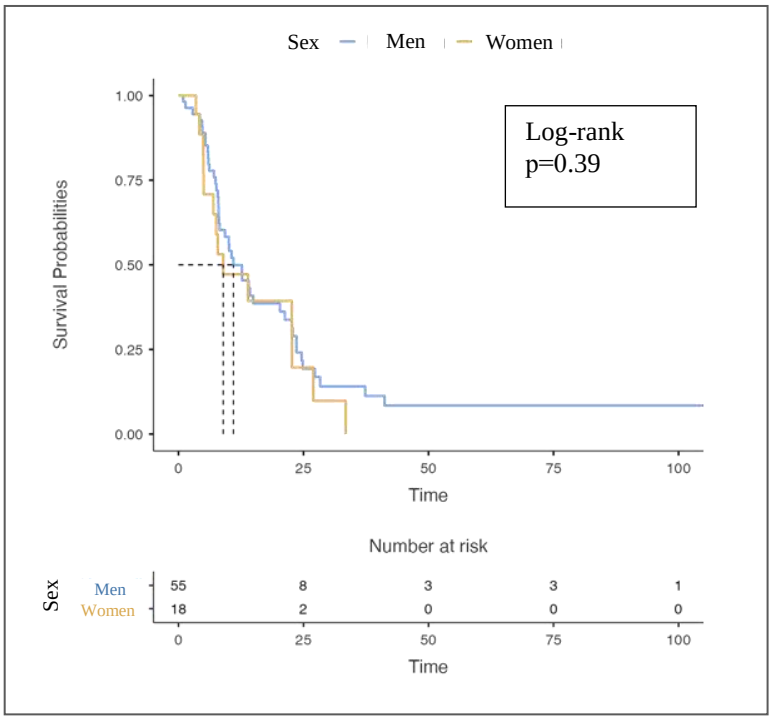


Figure 5.35 – Kaplan-Meier curves of OS indicators in patients with mRCC (N=73) without CN according to gender

Survival analysis revealed that the 3- and 5-year OS of mRCC patients without CN in men were 14.1% [6.6-29.8%, 95% CI] and 8.4% [3.0-23.8%, 95% CI], and the 1-year OS in women was 47.2% [28.6-78.1%, 95% CI], respectively. Meanwhile, the median OS was 11 [8.2-22.7, 95% CI] and 9 [7-NA, 95% CI] months, respectively. Thus, in this study, there was no advantage in OS and median OS according to gender in mRCC patients in the absence of CN (p=0.39).

In the patients included in the study, the frequency of renal lesions was approximately equal. As shown in Table 5.36, tumor of the left kidney was detected in 29 (39.7%) patients, on the right – 41 (56.2%) patients, bilateral lesions were diagnosed in 3 (4.1%) patients.

Table 5.36 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the location of the primary tumor

Localization of the primary tumor	Number of patients	HR
On the right	29 (39.7)	–
From left	41 (56.2)	0.80 (0.46-1.38, p=0.416)
Bilateral	3 (4.1)	0.45 (0.10-1.94, p=0.283)

Figure 5.36 shows that the 3-year and 5-year OS rates depending on the location of the patients' primary kidney tumor were 5.5% [0.8-36.3%, 95% CI] and 0% on the right, 11.8% [4.4-32.0%, 95% CI] and 7.9% [2.2-28.3%, 95% CI] on the left, and 33.3% [6.7-100.0%, 95% CI] and 33.3% [6.7-100.0%, 95% CI], respectively, when both kidneys were affected.

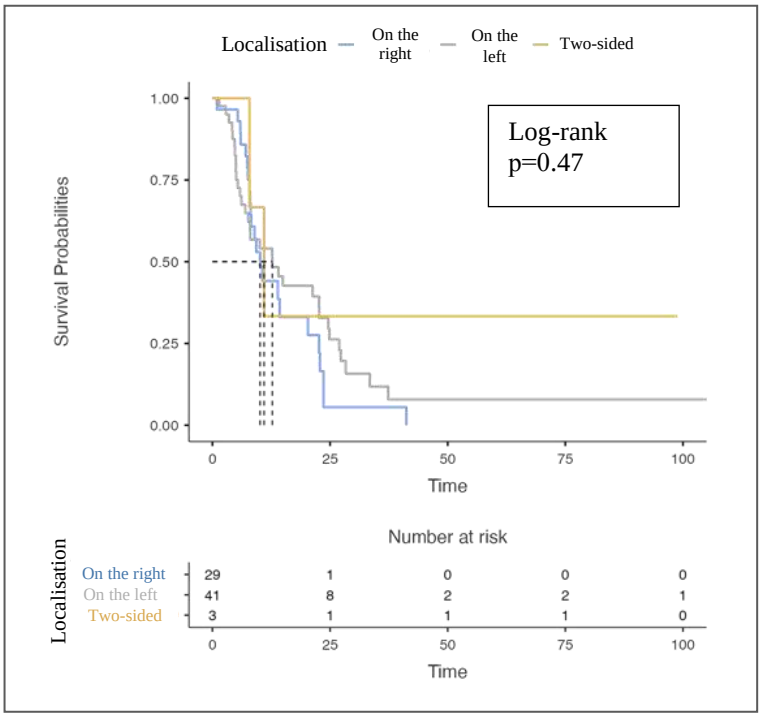


Figure 5.36 – Kaplan-Meier curves of OS indicators in patients with mRCC (N=73) without CN depending on the side of the primary tumor involved

Meanwhile, the median OS was 10.1 [8.1-22.7, 95% CI], 12.7 [7.6-24.6, 95% CI], and 11 [7.9-NA, 95% CI] months, respectively.

Thus, the study revealed no statistically significant differences in the rates of OS and median OS depending on the localization of the primary tumor in mRCC patients in the absence of CN (p=0.47).

When evaluating the mRCC patients at CN and metastasectomy included in the study according to ECOG status, Table 5.37 shows that patients with ECOG 2-3 somatic status predominated in 78% of cases.

Table 5.37 – Distribution of mRCC patients without CN according to ECOG status

ECOG	Number of patients	HR
ECOG0-1	16 (21.9)	–
ECOG2-3	57 (78.1)	6.93 (2.16-22.22, p=0.001)

The presented Kaplan-Meier curves (Figure 5.37) demonstrated that the 3-year and 5-year OS of patients with ECOG0-1 status were 56.0% [27.03-100.0%, 95% CI] and 56.0% [27.03-100.0%, 95% CI], while those with ECOG2-3 were 5.6% [1.85-16.7%, 95% CI] and 1.9% [0.27-12.9%, 95% CI], respectively. Meanwhile, the median OS at ECOG0-1 did not reach NA [22.7-NA, 95% CI], and at ECOG2-3 was 9 [7.9-13.9, 95% CI] months. Thus, the study revealed statistically significant differences in OS and median OS in mRCC patients in the absence of CN depending on ECOG status (p=0.00015).

Although we consider the factors included in the IMDC prognostic model separately, we evaluated the survival rates of mRCC patients without CN in the 2 prognostic groups in the overall cohort. Table 5.38 shows that of the 73 patients who did not undergo CN, 15 (20.5%) were in the favorable and intermediate prognosis groups and 58 (79.5%) were in the poor prognosis group. Thus, about 80% of patients were from the IMDC poor prognosis group.

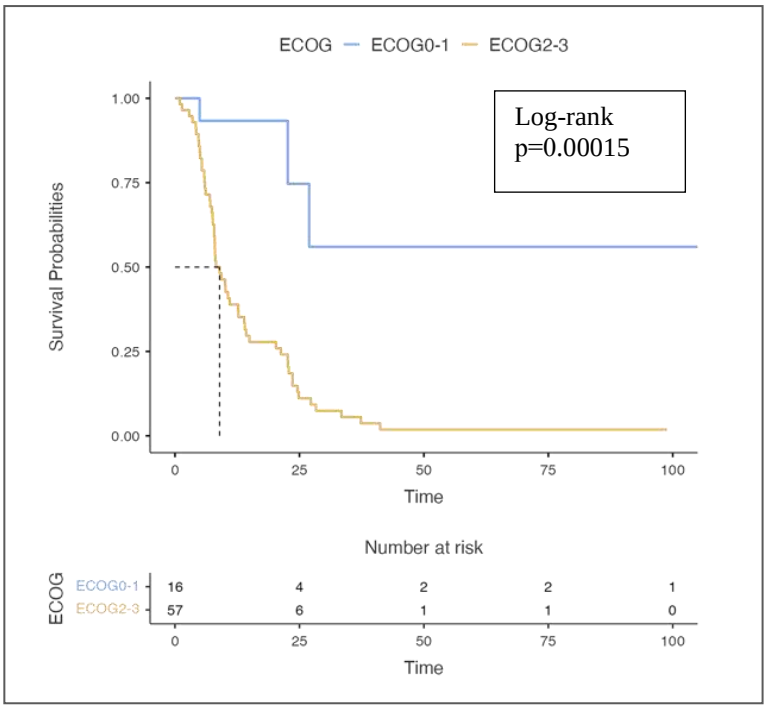


Figure 5.37 – Kaplan-Meier curves of OS indices in mRCC patients (N=73) in the absence of performing CN depending on ECOG status

Table 5.38 – Distribution of mRCC patients without CN according to IMDC prognosis

IMDC Forecast	Number of patients	HR
Favorable, intermediate	15 (20.5)	–
Poor	58 (79.5)	3.08 (1.44-6.61, p=0.004)

Figure 5.38 shows that the 3- and 5-year OS of patients in the absence of CN in the IMDC favorable and intermediate prognosis groups were 29% [11.1-74%, 95% CI] and 29% [11.1-74%, 95%] CI, and 6% [1.7-21%, 95% CI] and 0% for the poor prognosis, respectively. The median OS also differed and was 22.9 [21.3-NA, 95% CI] and 9 [7.9-13.9, 95% CI] months, respectively.

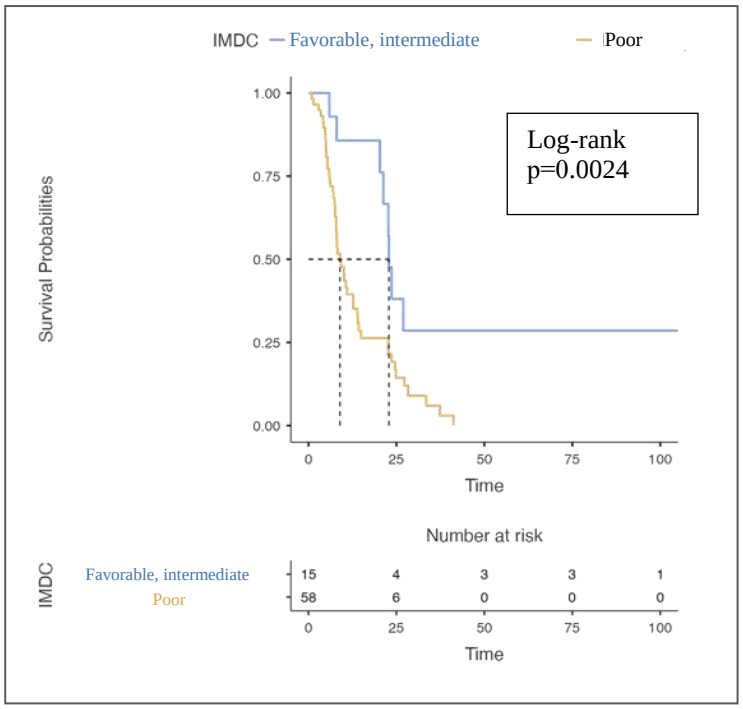


Figure 5.38 – Kaplan-Meier curves of OS indices in mRCC patients (N=73) in the absence of performing CN in IMDC prognostic groups

Thus, the study revealed statistically significant differences in OS and median OS depending on IMDC prognosis in mRCC patients in the absence of CN (p=0.0024).

5.3.2 Influence of tumor morphological characteristics on survival rates in patients with metastatic renal cell cancer in the absence of cytoreductive nephrectomy

When evaluating the mRCC patients included in the study according to the histologic variant, the majority of cases were verified as clear cell carcinoma – 59 (80.8%) patients. Non-small cell variants accounted for 14 (19.2%) cases (Table 5.39).

Table 5.39 – Distribution of mRCC patients without CN depending on the histological subtype of the primary tumor

Histology	Number of patients	HR
Clear-cell	59 (80.8)	–
Non- clear-cell	14 (19.2)	1.14 (0.59-2.19, p=0.706)

The presented Kaplan-Meier curve plot (Figure 5.39) shows that the 3-year and 5-year OS rates for luminal tumor variant were 9.7% [3.9-24.3%, 95% CI] and 4.8% [1.3-18.6%, 95% CI], and for non-small cell RCC 19.0% [6.0-60.3%, 95% CI] and 19.0% [6.0-60.3%, 95% CI], respectively. Meanwhile, the median OS was 12.7 [9-22.7, 95% CI] and 8 [5-NA, 95% CI] months, respectively. Thus, the study showed no statistically significant differences in OS and median OS depending on tumor histological subtype in mRCC patients without CN (p=0.7).

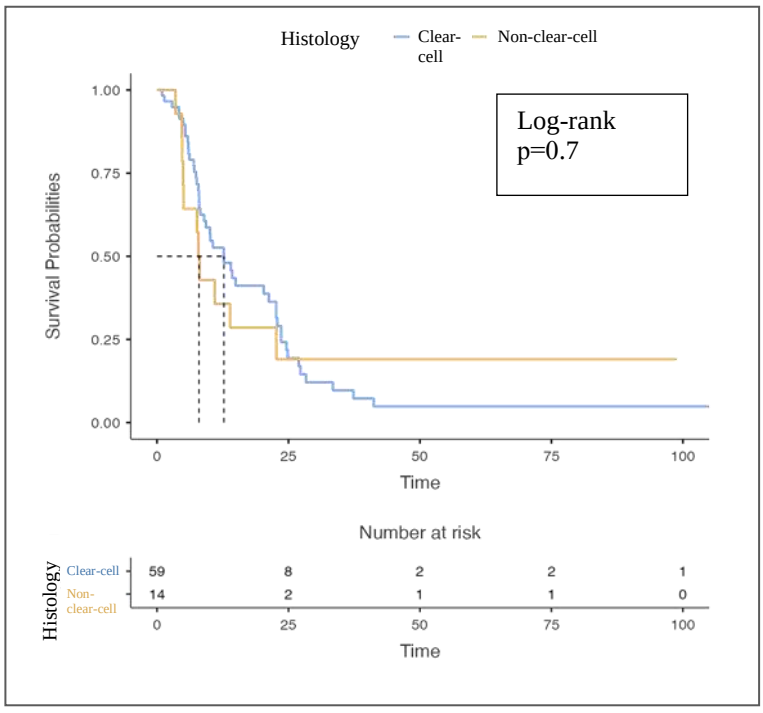


Figure 5.39 – Kaplan-Meier curves of OS indicators in patients with mRCC (N=73) without CN depending on the histological variant of the tumor

When evaluating the patients with mRCC included in the study depending on the degree of differentiation according to Fuhrman were distributed as follows.

Table 5.40 shows that the number of patients at G1 was 3 (4.1%), 20 (27.4%) at G2 and 50 (68.5%) at G3 in patients, respectively. Thus, 68.5% of the patients had low differentiated tumors.

Table 5.40 – Distribution of mRCC patients without CN according to Fuhrman's degree of tumor differentiation

Degree of differentiation	Number of patients	HR
Grade3	50 (68.5)	–
Grade1-2	23 (31.5)	0.26 (0.13-0.52, p<0.0001)

The presented Kaplan-Meier curves (Figure 5.40) show that the 3-year and 5-year OS rates at G1-2 and G3 were 35.67% [17.3-73.5%, 95% CI] and 26.75% [10.7-67.0%, 95% CI], 2.39% [0.3-16.5%, 95% CI] and 0%, respectively. Meanwhile, the median OS also differed and was 27 [22.7-NA, 95% CI] and 8.2 [7.9-12.7, 95% CI] months, respectively.

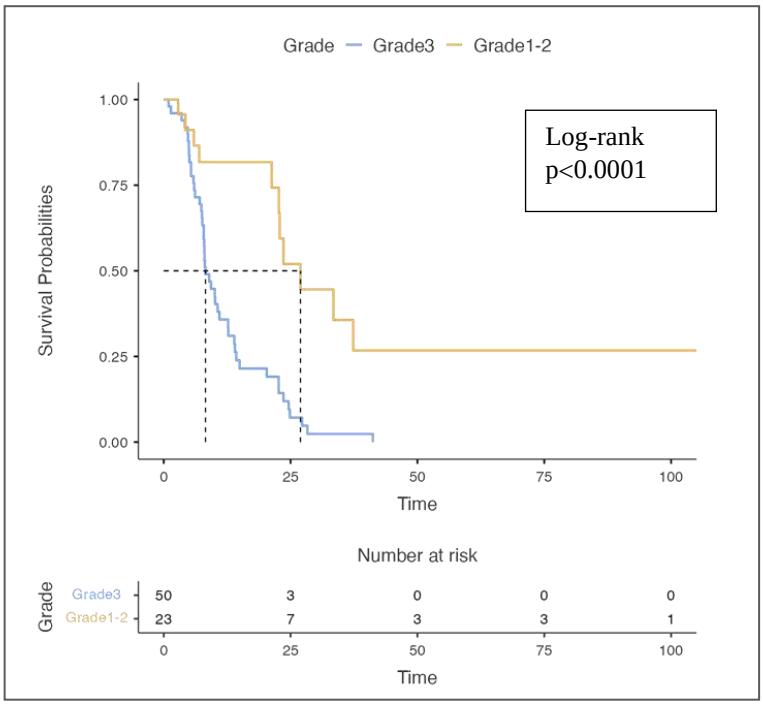


Figure 5.40 – Kaplan-Meier curves of OS indicators in patients with mRCC (N=73) without CN depending on the degree of tumor differentiation according to Fuhrman

Thus, our study revealed statistically significant differences in OB and median OB of mRCC patients in the absence of CN depending on the degree of tumor differentiation according to Fuhrman ($p<0.0001$).

Single metastases were detected in 8 (11%) and multiple metastases in 56 (89.0%) patients. As shown in Table 5.41, there were no patients with solitary metastases in this subgroup; patients with multiple metastases prevailed in 89% of cases.

Table 5.41 – Distribution of mRCC patients without CN depending on the number of metastases

Number of metastases	Number of patients	HR
Single	8 (11.0)	–
Multiple	65 (89.0)	2.51 (0.98-6.44, p=0.055)

As can be seen from Figure 5.41, the OS rates directly depend on the number of metastases. Thus, in patients with single and multiple metastases without CN, the 3- and 5-year OS rates were 41.7% [15.90-100.0%, 95% CI] and 20.8% [3.85-100.0%, 95% CI], 6.7% [2.26-19.6%, 95% CI] and 4.4% [1.16-17.0%, 95% CI], respectively. Meanwhile, the median OS also differed and was 33.4 [8-NA, 95% CI] and 10.6 [8.1-20.3, 95% CI] months, respectively.

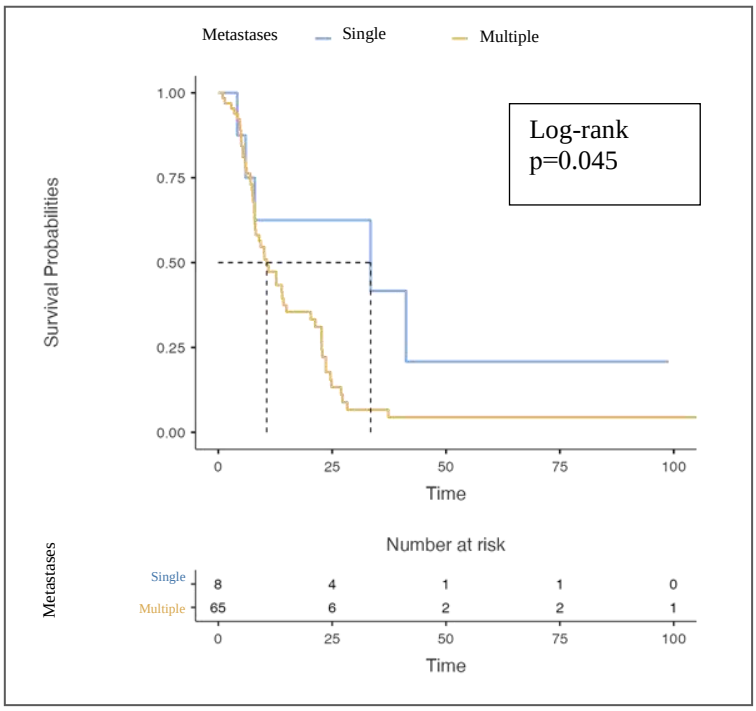


Figure 5.41 – Kaplan-Meier curves of OS indicators in patients with mRCC (N=73) without CN depending on the amount of metastasis

Thus, the study revealed statistically significant differences in the rates of OS and median OS in patients with mRCC in the absence of CN performance depending on the number of metastases ($p<0.0001$).

5.3.3 Impact of laboratory data on survival rates of patients with metastatic renal cell cancer in the absence of cytoreductive nephrectomy

When evaluating the patients included in the study depending on the hemoglobin level were distributed as follows. Thus, normal hemoglobin level was noted in 36 (49.3%) patients and anemia was noted in 37 (50.7%) patients. Thus, half of the mRCC patients in our study had anemia, as shown in Table 5.42.

Table 5.42 – Distribution of IRCC patients with absence of CN depending on hemoglobin level

Hemoglobin level	Number of patients	HR
Hemoglobin's normal	36 (49.3)	–
Anemia	37 (50.7)	2.24 (1.31-3.83, p=0.003)

The presented Kaplan-Meier curves (Figure 5.42) show that the 3-year and 5-year OS rates for normal hemoglobin were 18.4% [8.1-41.6%, 95% CI] and 9.2% [2.6-32.9%, 95% CI], respectively. In anemia, these rates decreased significantly to 3.7% [0.5-24.9%, 95% CI] and 3.7% [0.5-24.9%, 95% CI], respectively. The median OS also differed according to hemoglobin level and was 22.7 [14-27, 95% CI] and 8 [7-12.7, 95% CI] months, respectively.

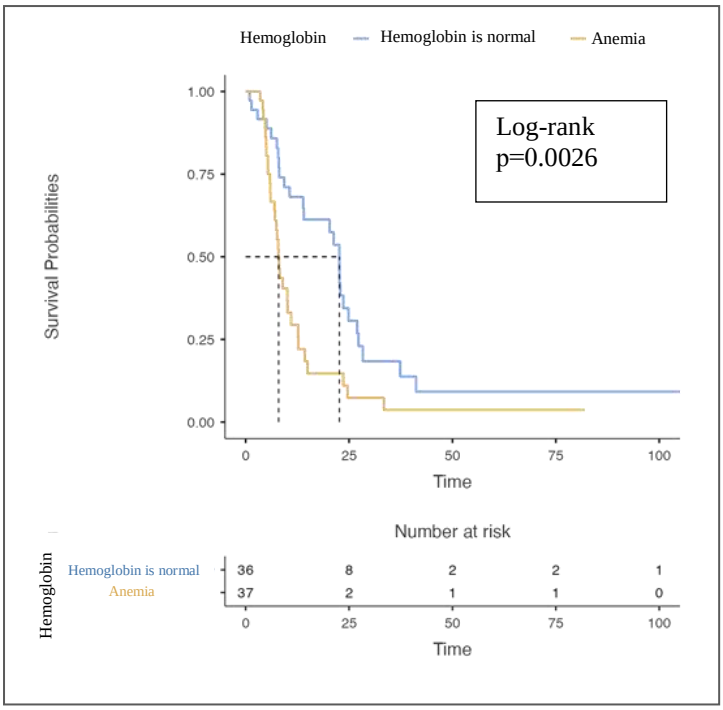


Figure 5.42 – Comparison of OS indicators of patients with mRCC (N=73) in the absence of CN depending on hemoglobin level

Thus, the conducted study revealed statistically significant differences in OB and median OS rates depending on hemoglobin level in mRCC patients in the absence of CN performance (p=0.0026).

When evaluating the patients included in the study depending on the level of alkaline phosphorus were distributed as follows. Thus, as can be seen from Table 5.43, a normal level of alkaline phosphorus was detected in 31 (42.5%) patients, and elevation of this index was observed in 42 (57.5%) patients. Thus, 2/3 of patients with mRCC had elevated alkaline phosphate levels.

Table 5.43 – Distribution of IRCC patients without CN depending on the level of alkaline phosphorus

Alkaline phosphatase level	Number of patients	HR
alkaline phosphorus is normal	31 (42.5)	–
alkaline phosphorus is elevated	42 (57.5)	1.20 (0.71-2.04, p=0.492)

Figure 5.43 shows that the 3-year and 5-year OS rates with normal alkaline phosphorus were 17.0% [7.1-40.5%, 95% CI] and 11.3% [3.5-36.9%, 95% CI], respectively. When alkaline phosphorus was elevated, these rates decreased to 7.1% [1.9-26.5%, 95% CI] and 3.5% [0.5-24.0%, 95% CI], respectively. The median OS was 10.6 [8.1-24.6, 95% CI] and 12.7 [7.9-22.7, 95% CI] months, respectively.

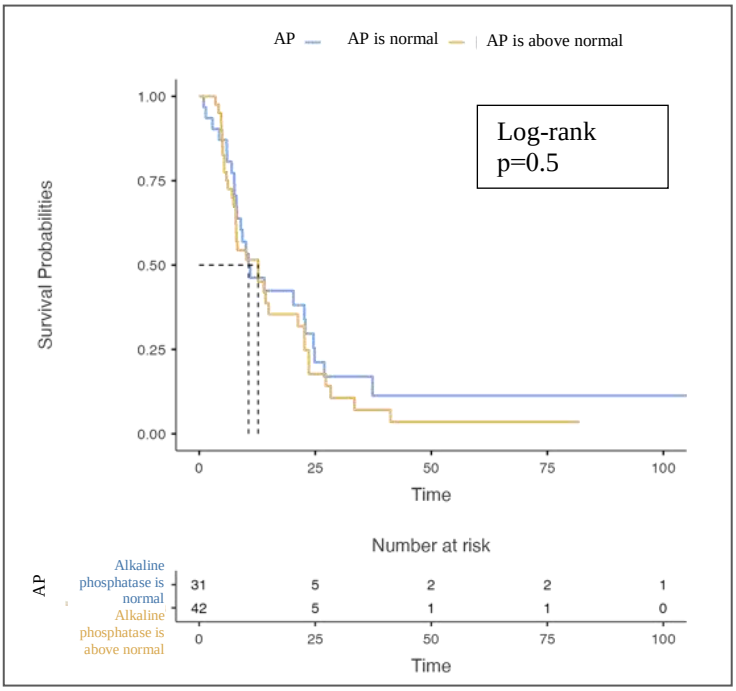


Figure 5.43 – Comparison of OS indicators of patients with mRCC (N=73) in the absence of CN fulfillment depending on the level of alkaline phosphorus

Thus, the study revealed no statistically significant differences in the rates of OS and median OS depending on the level of alkaline phosphate in patients with mRCC in the absence of CN (p=0.5).

When evaluating the patients included in the study depending on the level of LDH were distributed as follows. Thus, 42 (57.5%) patients had normal LDH levels, and elevation of this index was noted in 31 (42.5%) patients, as shown in Table 5.44.

Table 5.44 – Distribution of mRCC patients without CN depending on LDH level

LDH level	Number of patients	HR
LDH is normal	42 (57.5)	–
LDH is elevated	31 (42.5)	1.25 (0.74-2.11, p=0.411)

The presented Kaplan-Meier curves (Figure 5.44) show that the 3-year and 5-year OS rates for normal patients with LDH were 12.2% [4.65-32.19%, 95% CI] and 8.2% [2.32-28.62%, 95% CI], and for elevated LDH were 9.6% [2.65-34.67%, 95% CI] and 4.8% [0.72-31.73%, 95% CI], respectively. The median OS was 12.7 [8.1-23.6, 95% CI] and 10.1 [7.9-22.7, 95% CI] months, respectively.

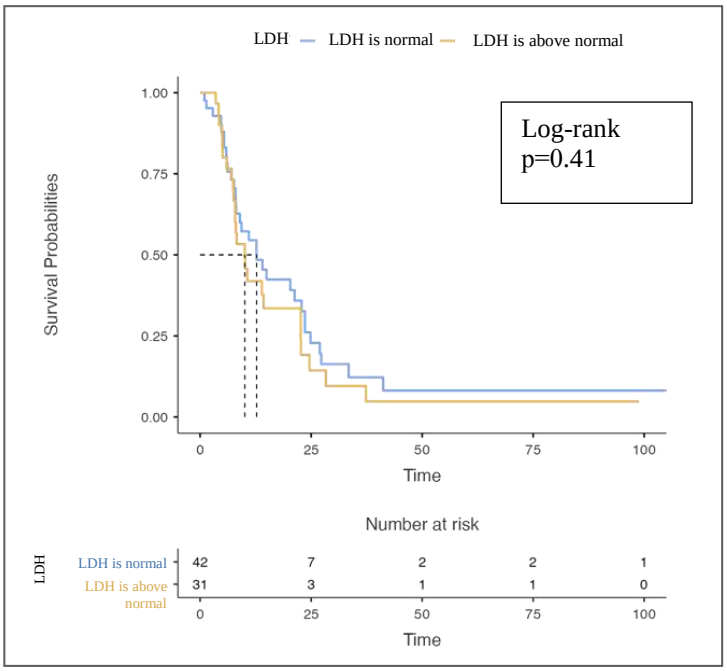


Figure 5.44 – Comparison of OS indicators of patients with mRCC (N=73) in the absence of CN depending on the level of LDH

Thus, the study did not reveal statistically significant differences in OS and median OS depending on LDH level in mRCC patients in the absence of CN performance (p=0.41).

5.3.4 Influence of metastases localization on survival rates of patients with metastatic renal cell cancer in the absence of cytoreductive nephrectomy

The distribution of mRCC patients without CN according to the presence of bone metastases is presented in Table 5.45.

Table 5.45 – Distribution of mRCC patients without CN depending on the presence of bone metastases

Bone metastasis	Number of patients	HR
Bone metastasis (-)	27 (37.0)	–
Bone metastases (+)	46 (63.0)	1.44 (0.82-2.52, p=0.202)

Survival analysis found that the 3-year and 5-year OS rates were 26.0% [12.8-52.7%, 95% CI] and 19.5% [7.9-48.2%, 95% CI] in the absence of bone metastases, and 3.1% [0.5-21.1%, 95% CI] and 0% in the presence of bone metastases, respectively. The median OS was 12.4 [8-37.3, 95% CI] and 10.1 [8-22.7, 95% CI] months, respectively (Figure 5.45).

Thus, the study did not reveal statistically significant differences in OS and median OS in patients with mRCC in the absence of CN in the absence/presence of bone metastases (p=0.2).

The distribution of mRCC patients without CN according to the presence of lung metastases is presented in Table 5.46.

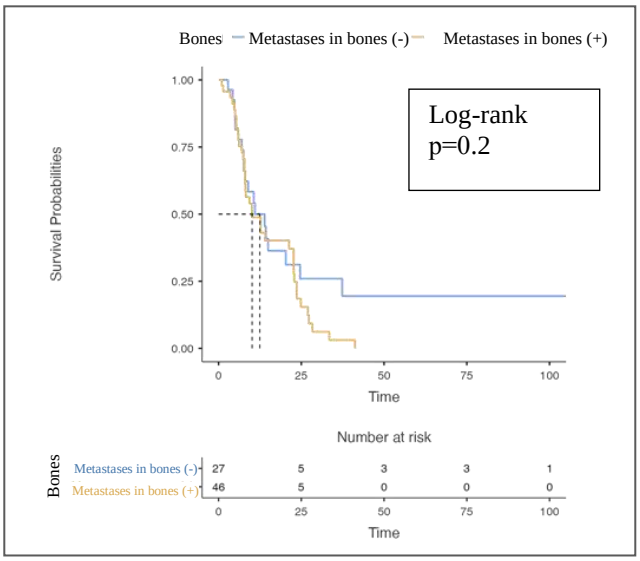


Figure 5.45 – Comparison of OS indicators of mRCC patients(N=73) with absence/presence of bone metastases in the absence of CN performance

Table 5.46 – Distribution of mRCC patients without CN depending on the presence of lung metastases

Lung metastasis	Number of patients	HR
Lung metastases (-)	23 (31.5)	–
Lung metastases (+)	50 (68.5)	1.16 (0.66-2.05, p=0.608)

The presented Kaplan-Meier curves (Figure 5.46) show that the 3-year and 5-year OS rates were 18.04% [5.93-54.8%, 95% CI] and 9.02% [1.53-53.3%, 95% CI] in the absence of lung metastases, and 8.14% [2.78-23.8%, 95% CI] and 5.43% [1.42-20.7%, 95% CI] in the presence of lung metastases, respectively. Meanwhile, the median OS was 13.9 [7.5-NA, 95% CI] and 11 [8.2-22.7, 95% CI] months, respectively. Thus, the study revealed no statistically significant differences in OS and median OS in patients with mRCC without CN in the absence of lung metastases (p=0.6).

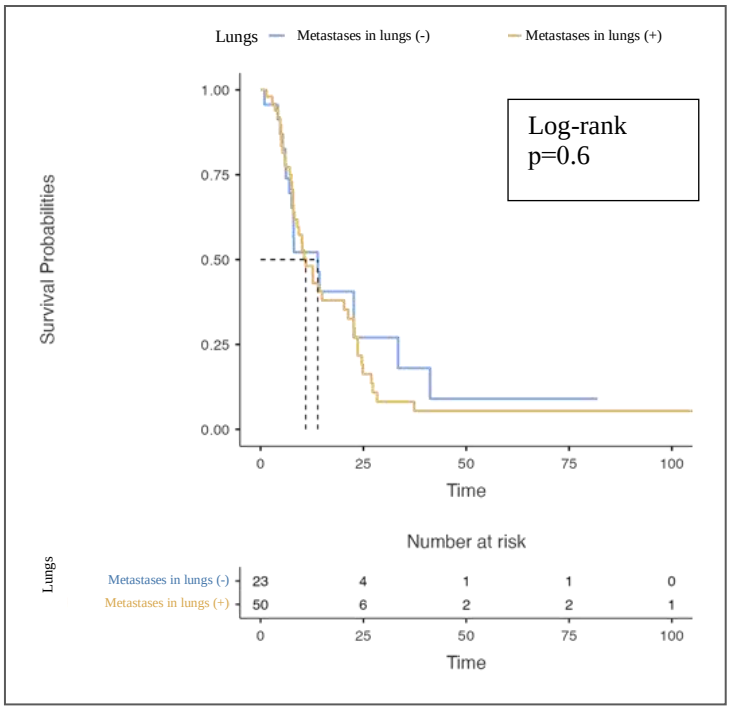


Figure 5.46 – Comparison of OS indicators of mRCC patients (N=73) with absence/presence of lung metastases in the absence of CN performance

The distribution of mRCC patients in the absence of CN according to the presence of liver metastases is presented in Table 5.47.

Table 5.47 – Distribution of mRCC patients without CN depending on the presence of liver metastases

Metastasis to the liver	Number of patients	HR
Metastasis to the liver (-)	52 (71.2)	–
Metastasis to the liver (+)	21 (28.8)	1.66 (0.94-2.93, p=0.083)

Figure 5.47 shows that the 3-year and 5-year OS rates in the absence of liver metastases were 14.1% [6.3-31.2%, 95% CI] and 8.4% [2.9-24.6%, 95% CI], and 0% in the presence of liver metastases, respectively. The median OS was 14 [9-22.9, 95% CI] and 8.2 [7.1-22.7, 95% CI] months, respectively.

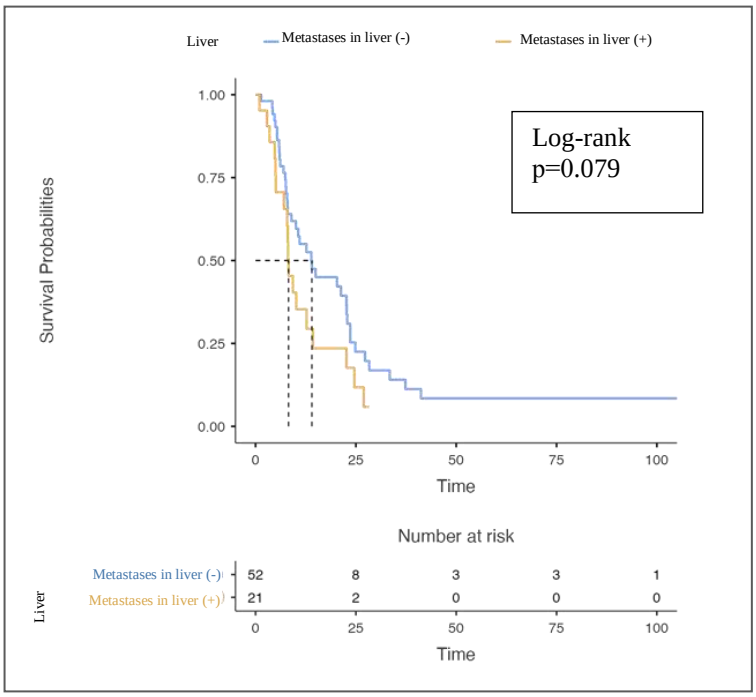


Figure 5.47 – Comparison of OS indicators of mRCC patients with absence/presence of liver metastases in the absence of CN fulfillment (N=73)

Thus, the study did not reveal statistically significant differences in OS and median OS in patients with mRCC in the absence of CN in the absence/ presence of liver metastases (p=0.079).

The distribution of mRCC patients without CN according to the presence of lymph node metastases is presented in Table 5.48.

Table 5.48 – Distribution of mRCC patients without CN depending on the presence of lymph node metastases

Metastasis to Lymph nodes	Number of patients	HR
Metastases to lymph nodes (-)	34 (46.6)	–
Metastases to lymph nodes (+)	39 (53.4)	1.61 (0.94-2.74, p=0.080)

Figure 5.48 shows that the 3-year and 5-year OS rates in the absence of lymph node metastases were 16.1% [6.10-42.7%, 95% CI] and 5.4% [0.83-35.0%, 95% CI], and in the presence of lymph node metastases 6.7% [1.79-25.0%, 95% CI] and 6.7%

[1.79-25.0%, 95% CI], respectively. The median OS was 21.3 [10.1-28.3, 95% CI] and 9 [7.9-13.9, 95% CI] months, respectively.

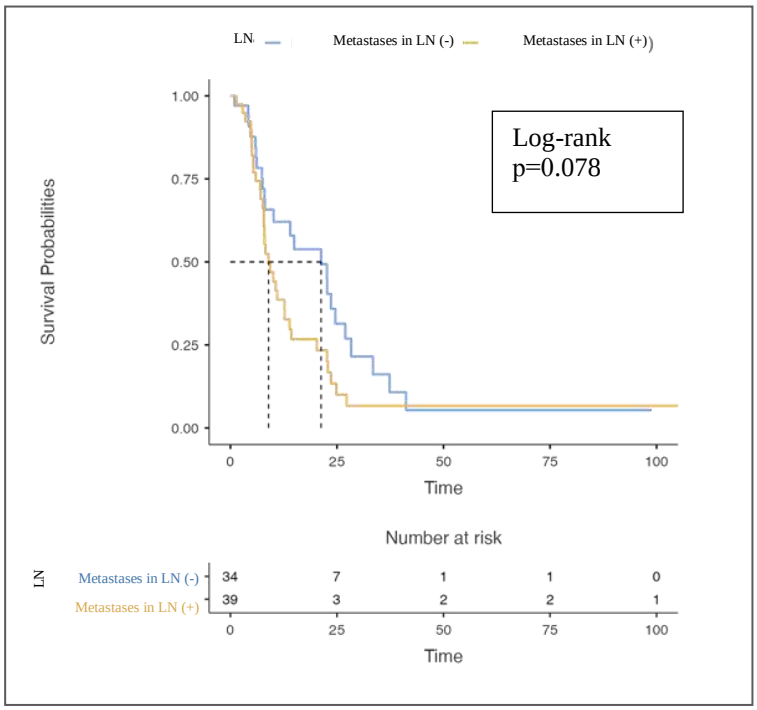


Figure 5.48 – Comparison of OS indicators of mRCC patients with absence/presence of metastases to lymph nodes in the absence of CN fulfillment (N=73)

Thus, the study revealed no statistically significant differences in the rates of OS and median OS in patients with mRCC in the absence of CN in the absence/ presence of lymph node metastases (p=0.078).

The distribution of mRCC patients undergoing CN and metastasectomy depending on the presence of brain metastases is presented in Table 5.49.

Table 5.49 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the presence of brain metastases

Metastasis to the brain	Number of patients	HR
Metastasis to the brain (-)	68 (93.2)	–
Metastases to the brain (+)	5 (6.8)	4.68 (1.61-13.59, p=0.005)

The presented Kaplan-Meier curves (Figure 5.49) show that the 3-year and 5-year OS rates in the absence of brain metastases were 11.7±1.3% and 7.1±1.2%, and 0% in the presence of brain metastases, respectively. Meanwhile, the median OS was 12.7 [9-22.7, 95% CI] and 7.4 [4.3-NA, 95% CI] months, respectively.

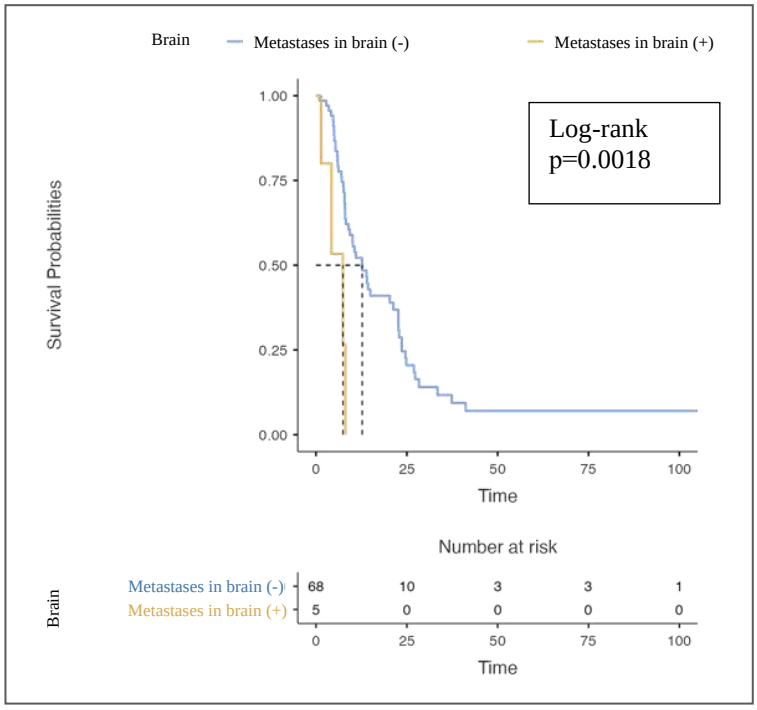


Figure 5.49 – Comparison of OS indicators of mRCC patients with absence/presence of brain metastases in the absence of CN fulfillment (N=73)

Thus, the study revealed statistically significant differences in OS and median OS in mRCC patients in the absence of CN in the absence/ presence of brain metastases (p=0.0019).

For this subgroup of mRCC patients, we performed Cox single and multivariate analyses. The data are presented in Table 5.50.

Table 5.50 – Cox proportional hazards model of the effect on OS outcomes in the group of patients who did not undergo CN (N=73)

Factors	Gradations	Number	HR (single-factor)	HR (multivariate)
Gender	men	55 (75.3)	–	–
	women	18 (24.7)	1.31 (0.71-2.40, p=0.391)	2.39 (0.71-8.06, p=0.160)
Age	18-44	2 (2.7)	–	–
	45-59	34 (46.6)	1.45 (0.19-10.80, p=0.716)	2.49 (0.21-29.15, p=0.467)
	60-74	33 (45.2)	1.60 (0.22-11.84, p=0.647)	1.22 (0.11-13.98, p=0.872)
	over 75	4 (5.5)	1.84 (0.20-16.67, p=0.588)	1.80 (0.08-40.22, p=0.711)
Localization	on the right	29 (39.7)	–	–
	on the left	41 (56.2)	0.80 (0.46-1.38, p=0.416)	1.42 (0.65-3.09, p=0.381)
	bilateral	3 (4.1)	0.45 (0.10-1.94, p=0.283)	0.99 (0.14-6.84, p=0.995)
Histologic variant	Clear-cell	59 (80.8)	–	–
	non- clear-cell	14 (19.2)	1.14 (0.59-2.19, p=0.706)	1.58 (0.53-4.77, p=0.414)
Degree tumor differentiation by Fuhrman	3	50 (68.5)	–	–
Degree tumor differentiation by Fuhrman	1-2	23 (31.5)	0.26 (0.13-0.52, p<0.001)	0.48 (0.22-1.04, p=0.062)
Number of metastases	single	8 (11.0)	–	–
	multiple	65 (89.0)	2.51 (0.98-6.44, p=0.055)	7.29 (0.83-64.02, p=0.073)

Continuation of Table 5.50

Factors	Gradations	Number	HR (single-factor)	HR (multivariate)
Bones	bone mts (-)	27 (37.0)	–	–
	bone mts (+)	46 (63.0)	1.44 (0.82-2.52, p=0.202)	1.63 (0.64-4.16, p=0.308)
Lungs	mts to the lungs (-)	23 (31.5)	–	–
	mts to the lungs (+)	50 (68.5)	1.16 (0.66-2.05, p=0.608)	0.42 (0.16-1.08, p=0.071)
Liver	mts to the liver (-)	52 (71.2)	–	–
	mts to the liver (+)	21 (28.8)	1.66 (0.94-2.93, p=0.083)	1.38 (0.55-3.47, p=0.488)
Lymph nodes	mts in lymph nodes (-)	34 (46.6)	–	–
	mts in lymph nodes (+)	39 (53.4)	1.61 (0.94-2.74, p=0.080)	1.99 (0.80-4.98, p=0.141)
Brain	brain mts (-)	68 (93.2)	–	–
	mts to the brain	5 (6.8)	4.68 (1.61-13.59, p=0.005)	8.53 (1.84-39.45, p=0.006)
Hemoglobin	hemoglobin is normal	36 (49.3)	–	–
	anemia	37 (50.7)	2.24 (1.31-3.83, p=0.003)	2.74 (0.91-8.28, p=0.074)
Alkaline phosphatase	alkaline phosphorus is normal	31 (42.5)	–	–
	alkaline phosphorus is elevated	42 (57.5)	1.20 (0.71-2.04, p=0.492)	0.53 (0.22-1.29, p=0.165)
LDH	LDH is normal	42 (57.5)	-	-
	LDH is elevated	31 (42.5)	1.25 (0.74-2.11, p=0.411)	1.12 (0.51-2.45, p=0.777)
ESR	ESR's normal	9 (12.3)	–	–
	ESR is elevated	64 (87.7)	2.11 (0.84-5.31, p=0.113)	3.21 (0.85-12.10, p=0.085)
Platelets	platelets normally	39 (53.4)	–	–

Continuation of Table 5.50

Factors	Gradations	Number	HR (single-factor)	HR (multivariate)
	thrombocytosis	19 (26.0)	2.20 (1.17-4.14, p=0.014)	0.67 (0.24-1.89, p=0.446)
	thrombocytopenia	15 (20.5)	1.13 (0.57-2.23, p=0.730)	0.58 (0.18-1.89, p=0.370)
ECOG status	ECOG 0-1	16 (21.9)	–	–
	ECOG 2-3	57 (78.1)	6.93 (2.16-22.22, p=0.001)	4.13 (1.22-14.01, p=0.023)
The drug in line 1	TKI	63 (86.3)	–	–
	IO	10 (13.7)	0.19 (0.03-1.36, p=0.098)	0.84 (0.07-9.36, p=0.885)
Metastasectomy	metastasectomy (-)	64 (87.7)	–	–
	metastasectomy (+)	9 (12.3)	0.78 (0.33-1.83, p=0.570)	1.45 (0.28-7.59, p=0.663)
Radiation therapy	radiation therapy (-)	64 (87.7)	–	–
	radiation therapy (+)	9 (12.3)	1.17 (0.55-2.48, p=0.687)	0.61 (0.17-2.20, p=0.446)

In the single-factor analysis, the degree of tumor differentiation according to Fuhrman, ECOG status and the presence of brain metastases, hemoglobin and platelet levels were the factors influencing the RR. In multivariate ECOG status and brain metastases were additional factors influencing the OS in patients who did not undergo CN.

5.4 Evaluation of forecast factors and their impact on efficiency when performing metastasectomy in patients with metastatic renal cell cancer

Further we considered clinical, laboratory, pathomorphologic factors influencing the OS of 226 patients with mRCC who underwent metastasectomy.

The most frequent cytoreductive interventions were lung resection or lobectomy – 64 (28,3%), resection of femur, iliac, humerus or ribs – 32 (14,2%), endoprosthesis or osteosynthesis of bones – 26 (11,5%), vertebroplasty – 24 (10,6%), removal of recurrence in the kidney bed and laminectomy – 23 (10,2%), respectively.

5.4.1 Survival rates of patients depending on the from clinical characteristics in the performance of metastasectomies

The presented Kaplan-Meier curves (Figure 5.50) show that the 3- and 5-year OS of patients undergoing metastasectomy were 60% [54-67%, 95% CI] and 43% [37-51%, 95% CI], respectively. The median OS was 49.6 [41.8-60.8, 95% CI] months.

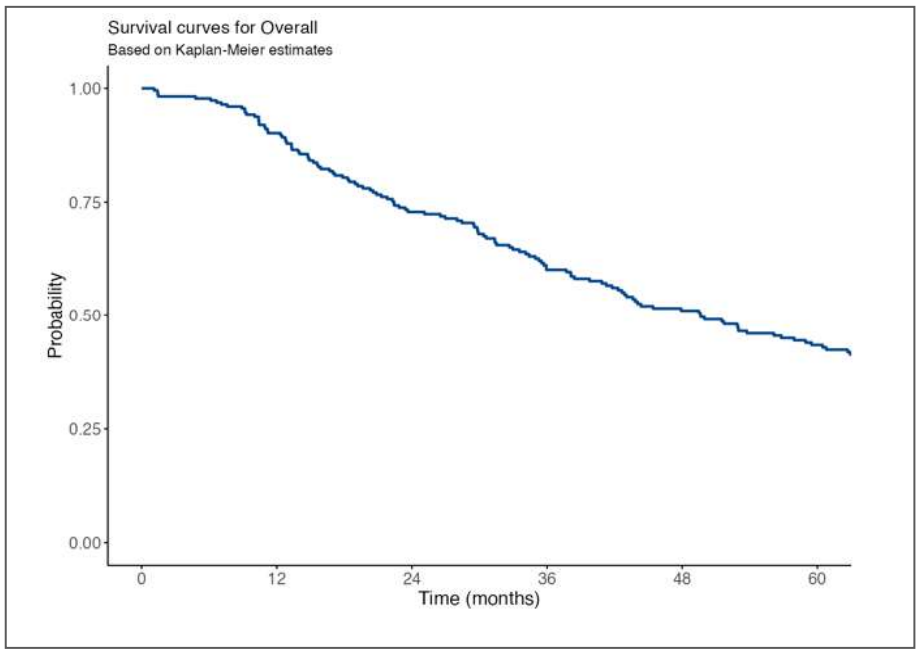


Figure 5.50 – OS indicators of mRCC patients (N=226) when performing a metastasectomy

In evaluating the mRCC patients at metastasectomy included in the study, it was found that the study was male dominated with 63.3% of cases (Table 5.51).

Table 5.51 – Distribution of mRCC patients undergoing metastasectomy according to gender characteristics

Gender	Number of patients	HR
Men	143 (63.3)	–
Women	83 (36.7)	0.87 (0.64-1.19, p=0.381)

Figure 5.51 shows that the 3- and 5-year OS rates of mRCC patients when metastasectomy was performed were 57.5% [49.8-66.5%, 95% CI] and 41.6% [34,0-51.0%, 95% CI], 64.7% [54.8-76.4%, 95% CI], and 46.5% [36.4-59.5%, 95% CI], respectively With a median OS of 43.8 [35.9-65.7, 95% CI] and 56.8 [43.6-69, 95% CI] months, respectively.

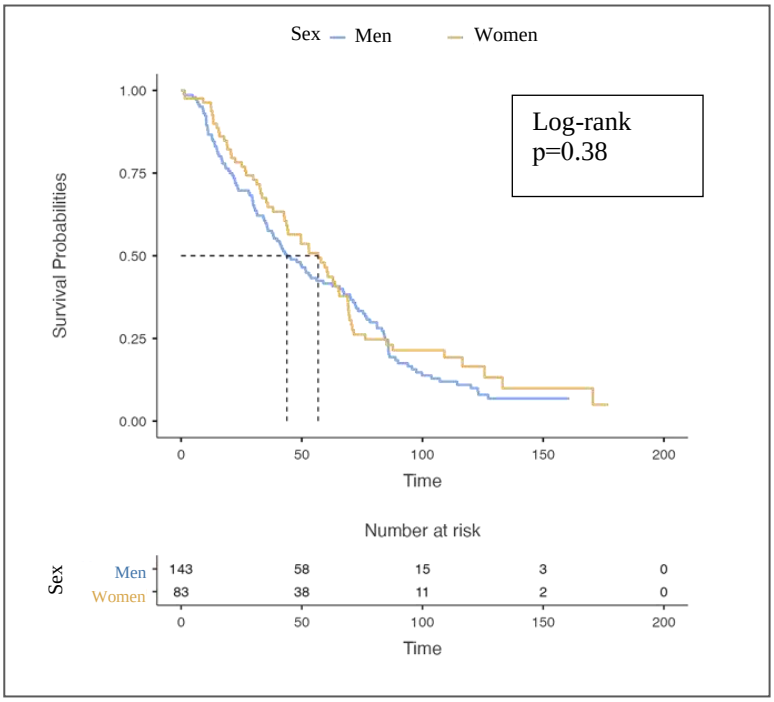


Figure 5.51 – Kaplan-Meier curves of OS indicators in mRCC patients (N=226) when performing metastasectomy according to gender

Thus, in the present study, there was no advantage in OS and median OS rates according to gender in mRCC patients when metastasectomy was performed (p=0.38).

The mean age of the patients was 58.8±9.4 years (28-80 years). Less than 60 years were 116 (51.3%) and more than 60 years were 110 (48.7%) patients. When evaluating the mRCC patients included in the study, it was found that the study was dominated by patients in the age range of 45-59 years in 46% (Table 5.52).

Table 5.52 – Distribution of mRCC patients without CN according to age

Age	Number of patients	HR
18-44	16 (7.1)	–
45-59	104 (46.0)	0.64 (0.37-1.11, p=0.112)
60-74	95 (42.0)	0.68 (0.39-1.19, p=0.177)
over 75	11 (4.9)	1.14 (0.51-2.55, p=0.741)

The presented Kaplan-Meier curve diagram (Figure 5.52) shows that the 3-year and 5-year OS rates at ages 18-44 years were 60.58% [40.32-91.00%, 95% CI] and 33.65% [16.51-68.60%, 95% CI], respectively, at ages 45-59 years, 58.59% [49.60-69.20%, 95% CI] and 44.47% [35.53-55.66%, 95% CI], at ages 60-74 years, 63.85% [54.55-74.75%, 95% CI] and 45.17% [35.65-57.24%, 95% CI], respectively. And the 3-year and 5-year OS rates in patients older than 75 years were 42.42% [20.63-87.24%, 95% CI] and 31.82% [12.73-79.55%, 95% CI], respectively. Meanwhile, the median OS was 49.5 [20.6-78.2, 95% CI], 47.9 [35.9-65.7, 95% CI], 56.1 [42.6-69.5, 95% CI], and 34.4 [10.4-NA, 95% CI] months, respectively.

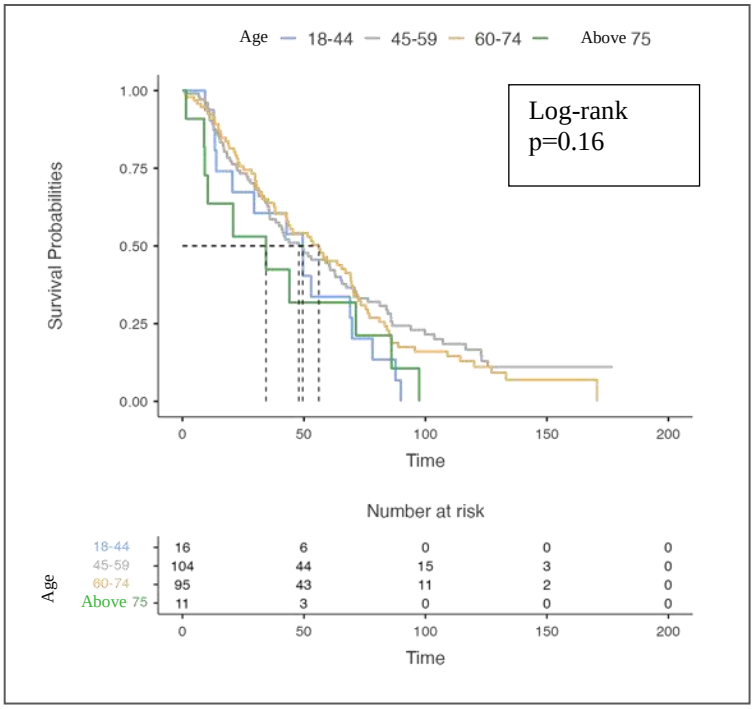


Figure 5.52 – Kaplan-Meier curves of OS rates in mRCC patients (N=226) when metastasectomy was performed as a function of age (N=226)

Thus, in the present study, there was no advantage in OS and median OS rates according to age in mRCC patients when metastasectomy was performed (p=0.16).

In the patients included in the study, the frequency of renal lesions was approximately equal. As shown in Table 5.53, left kidney tumor was detected in 121 (53.5%) patients, in 100 (44.3%) patients on the right side, and bilateral lesions were diagnosed in 5 (2.2%) patients.

Table 5.53 – Distribution of mRCC patients undergoing CN and metastasectomy depending on the location of the primary tumor

Localization of the primary tumor	Number of patients	HR
On the right	121 (53.5)	–
From left	100 (44.2)	0.90 (0.66-1.21, p=0.465)
Bilateral	5 (2.2)	0.62 (0.20-1.97, p=0.421)

Figure 5.53 shows that the 3-year and 5-year OS rates depending on the location of the patients' primary kidney tumor were 56.8% [48.3-66.75%, 95% CI] on the right and 40,5% [32.2-50.86%, 95% CI], on the left – 62.2% [53.1-72.80%, 95% CI] and 45.5% [36.3-56.88%, 95% CI], when both kidneys were affected -100.0% [100.0-100.00%, 95% CI] and 75.0% [42.6-100.00%, 95% CI], respectively. Meanwhile, the median OS was 43.6 [35.5-60.5, 95% CI], 53 [42.3-69.3, 95% CI], and 84.2 [42.9-NA, 95% CI] months, respectively. Thus, the study revealed no statistically significant differences in OS and median OS depending on primary tumor location in mRCC patients undergoing metastasectomy (p=0.59).

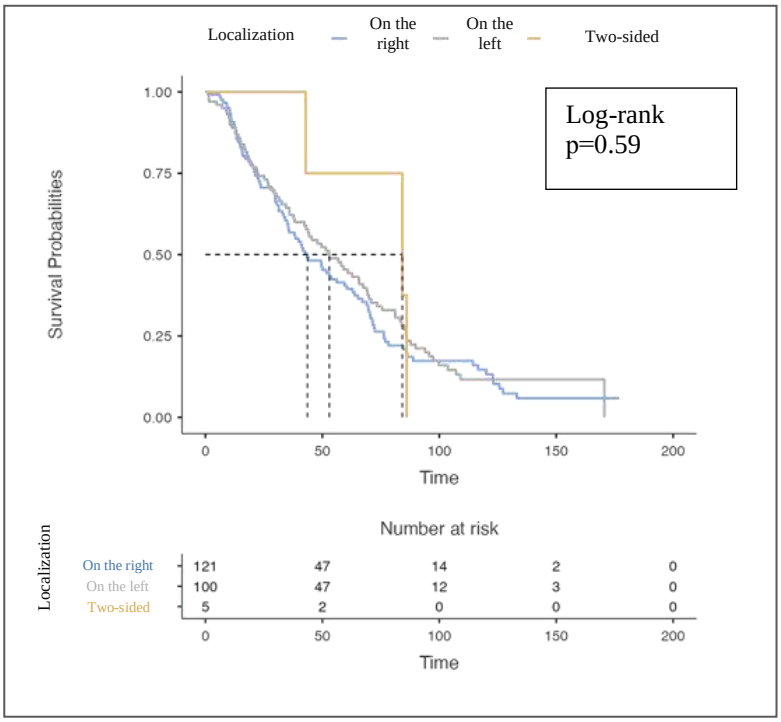


Figure 5.53 – Kaplan-Meier curves of OS indicators in mRCC patients (N=226) when performing metastasectomy depending on the side of the primary tumor involved

When evaluating the mRCC patients at metastasectomy included in the study according to ECOG status, Table 5.54 shows that patients with ECOG 1-2 somatic status predominated in 78.7% of cases.

Table 5.54 – Distribution of mRCC patients undergoing metastasectomy according to ECOG status

ECOG status	Number of patients	HR
ECOG0	16 (7.1)	–
ECOG1	97 (42.9)	0.95 (0.51-1.77, p=0.878)
ECOG2	81 (35.8)	2.09 (1.13-3.86, p=0.019)
ECOG3	32 (14.2)	6.88 (3.44-13.76, p<0.001)

The presented Kaplan-Meier curves (Figure 5.54) demonstrated that the 3-year and 5-year OS rates of patients with ECOG0 status were 92.31% [78.9-100.0%, 95% CI] AND 84.62% [67.1-100.0%, 95% CI], with ECOG1 79,11% [70.9-88.2%, 95% CI] AND 63.47% [53.8-74.9%, 95% CI], with ECOG2 50.23% [40.4-62.5%, 95% CI] AND 30.14% [21.6-42.1%, 95% CI], and with ECOG3 18.75% [9.1-38.6%, 95% CI] AND 4.69% [0.8-27.1%, 95% CI], respectively. Meanwhile, the median OS also differed and was 81.1 [69.5-NA, 95% CI], 73.4 [63.7-85.9, 95% CI], 38.1 [29.8-49.6, 95% CI], and 14.6 [11.2-29.5, 95% CI] months, respectively.

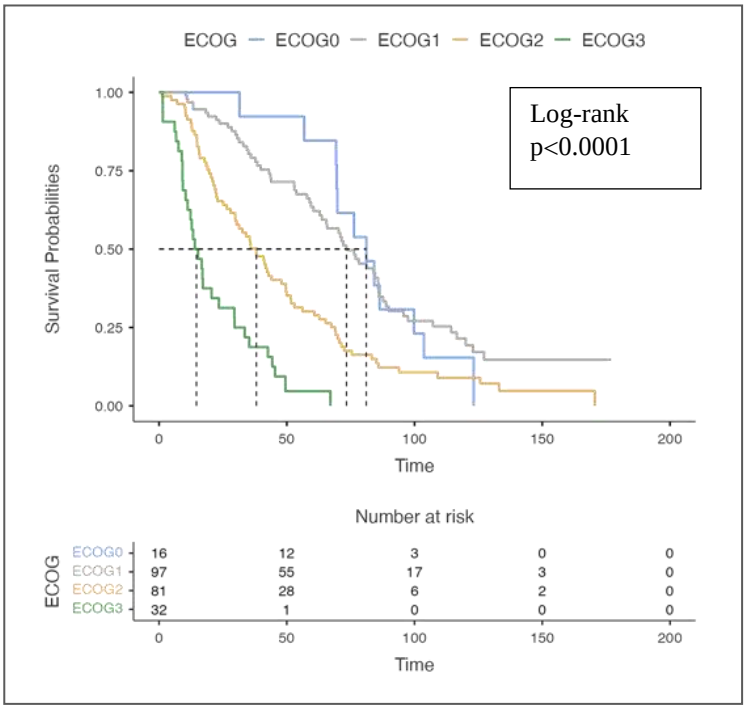


Figure 5.54 – Kaplan-Meier curves of OS rates in mRCC patients (N=226) undergoing metastasectomy depending on ECOG status

Thus, the study revealed statistically significant differences in the OS and median OS rates in mRCC patients undergoing metastasectomy depending on ECOG status ($p<0.0001$).

Although we consider the factors included in the IMDC prognostic model separately, we evaluated the survival rates of mRCC patients undergoing metastasectomy in 3 prognostic groups in the overall cohort. Table 5.55 shows that of the 226 patients who underwent metastasectomy, 75 (33.2%) patients were in the favorable prognosis group, 79 (34.9%) in the intermediate prognosis group, and 72 (31.9%) patients in the poor prognosis group. Thus, more than 75% of patients were from the intermediate and poor prognosis groups according to IMDC.

Table 5.55 – Distribution of mRCC patients undergoing CN and metastasectomy according to IMDC prognosis

IMDC Forecast	Number of patients	HR
Favorable	75 (33.2)	–
Intermediate	79 (35.0)	2.23 (1.52-3.27, $p<0.001$)
Poor	72 (31.9)	3.83 (2.65-5.55, $p<0.001$)

Figure 5.55 shows that the 3- and 5-year OS rates of patients undergoing metastasectomy in the IMDC favorable, intermediate, and poor prognosis groups were 83,9% [76.0-92.68%, 95% CI] and 75.7% [66.5-86.12%, 95% CI], 57.8% [47.1-70.85%, 95% CI] and 28.1% [18.8-41.90%, 95% CI], 36.0% [26.2-49.54%, 95% CI] and 21.3% [13.3-34.16%, 95% CI], respectively. Meanwhile, the median OS also differed and was 84.5 [72.2-88.8, 95% CI], 41.8 [35.7-51.5, 95% CI], and 20.9 [16.7-35.3, 95% CI] months, respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on IMDC prognosis in mRCC patients undergoing metastasectomy ($p<0.0001$).

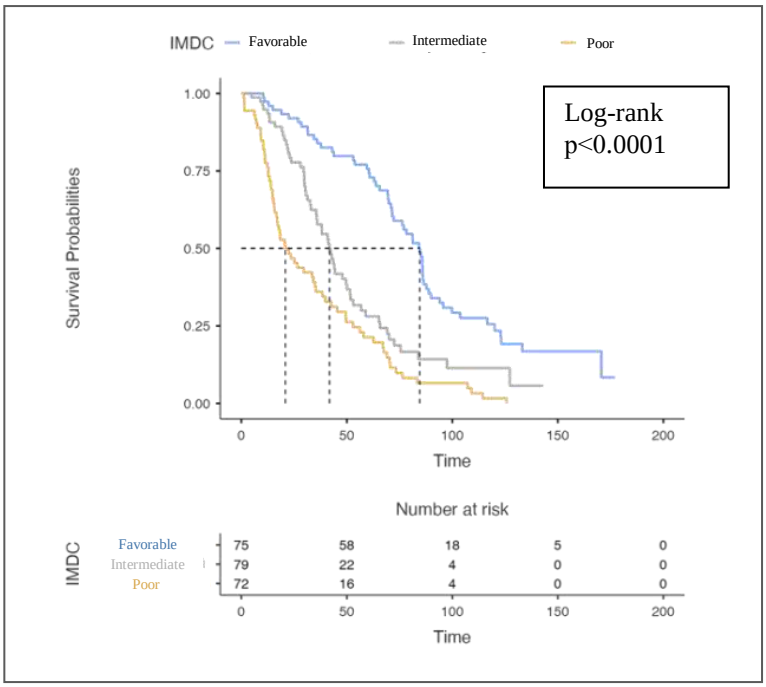


Figure 5.55 – Kaplan-Meier curves of OS indices in mRCC patients (N=226) at metastasectomy in IMDC prognostic groups

5.4.2 Influence of tumor morphological characteristics on survival rates in patients with metastatic renal cell carcinoma in the performance of metastasectomy

When evaluating the mRCC patients included in the study depending on the histologic variant, 213 (94.2%) patients were verified as having clear cell carcinoma in the majority of cases. Non-small cell variants accounted for 13 (5.8%) cases (Table 5.56).

Table 5.56 – Distribution of mRCC patients undergoing metastasectomy depending on the histological variant of the tumor

Histologic variant	Number of patients	HR
Clear-cell	213 (94.2)	–
Non- clear-cell	13 (5.8)	1.15 (0.61-2.19, p=0.659)

The presented Kaplan-Meier curve plot (Figure 5.56) shows that the 3-year and 5-year OS rates for luminal tumor variant were 61.3% [54.9-68.4%, 95% CI] and 44.5% [38.0-52.2%, 95% CI], and for non-small cell RCC were 41.7% [21.3-81.4%, 95% CI] and 25.0% [9.4-66.6%, 95% CI], respectively. Meanwhile, the median OS was 51.7 [42.6-62.9, 95% CI] and 32.8 [14.9-NA, 95% CI] months, respectively.

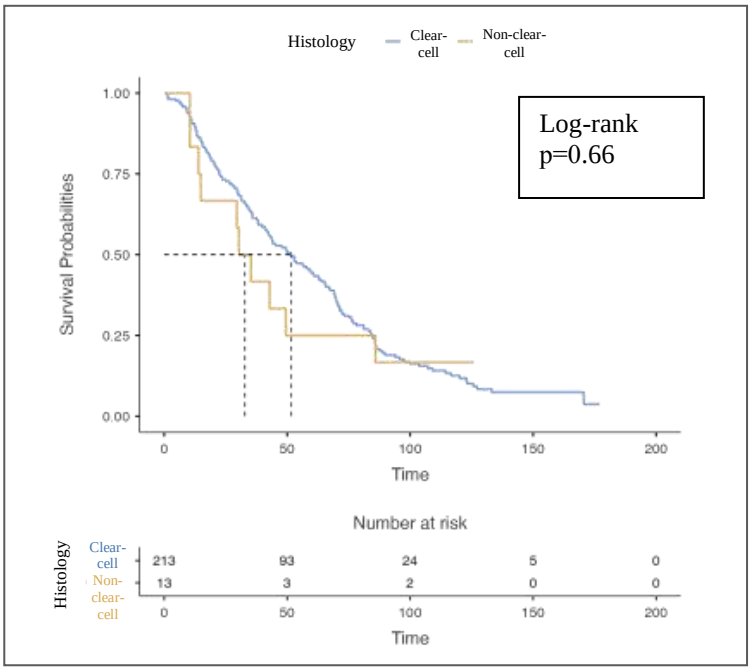


Figure 5.56 – Kaplan-Meier curves of OS indicators in mRCC patients (N=226) when performing metastasectomy depending on the histological variant of the tumor

Thus, the conducted study did not reveal statistically significant differences in OS and median OS rates depending on the histological subtype of tumor in mRCC patients when metastasectomy was performed (p=0.66).

When evaluating the patients included in the study depending on the degree of differentiation according to Fuhrman were distributed as follows. Table 5.57 shows that the number of patients with G1 was 61 (27%), G2 – 88 (38.9%) and G3 – in 77 (34.1%) patients, respectively. Thus, Fuhrman grade G2 and G3 tumors were found in 73% of patients.

Table 5.57 – Distribution of mRCC patients undergoing metastasectomy according to Fuhrman tumor differentiation

Degree of tumor differentiation	Number of patients	HR
Grade 1	61 (27.0)	–
Grade 2	88 (38.9)	2.24 (1.52-3.30, p<0.001)
Grade 3	77 (34.1)	3.19 (2.17-4.70, p<0.001)

The presented Kaplan-Meier curves (Figure 5.57) shows that the 3-year and 5-year OS rates depending on tumor differentiation according to Fuhrman were 88.2% [80.3-96,80%, 95% CI] and 77.6% [67.6-89.14%, 95% CI], 59.0% [48.9-71.11%, 95% CI] and 35.5% [25.9-48.59%, 95% CI], 38.7% [29.1-51.58%, 95% CI] and 23.4% [15.5-35.50%, 95% CI], respectively. Meanwhile, the median OS also differed and was 84.2 [72.2-97.4, 95% CI], 44 [35.9-57.9, 95% CI], and 29.5 [20.3-40.9, 95% CI] months, respectively.

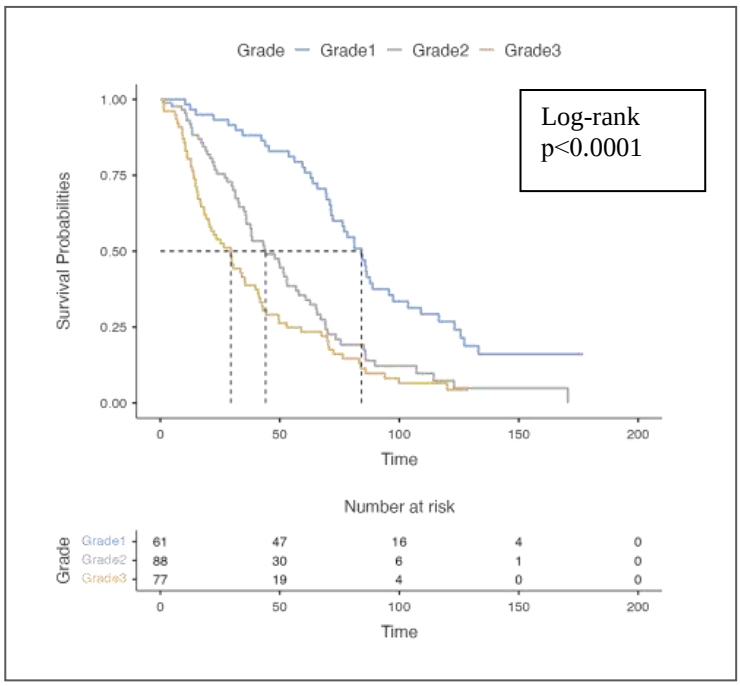


Figure 5.57 – Kaplan-Meier curves of OS indicators of mRCC patients when performing metastasectomy (N=226) depending on tumor differentiation according to Fuhrman

Thus, our study revealed statistically significant differences in OS and median OS of mRCC patients when performing metastasectomy depending on the degree of tumor differentiation according to Fuhrman ($p<0.0001$).

When evaluating the patients with mRCC included in the study depending on the type of metastases were distributed as follows. Table 5.58 shows that the number of patients with synchronous metastases was 71 (31.4%) patients and 155 (68.6%) patients with metachronous metastases, respectively. Thus, patients with metachronous metastases predominated in 68.6% of cases.

Table 5.58 – Distribution of mRCC patients undergoing metastasectomy depending on the type of metastases

Type of metastasis	Number of patients	HR
Synchronous	71 (31.4)	–
Metachronous	155 (68.6)	0.52 (0.38-0.71, $p<0.001$)

The presented Kaplan-Meier curves of the patients in Figure 5.58 show that the 3-year and 5-year OS depending on the type of metastases were 66.5% [59.2-74.63%, 95% CI] and 51.5% [43.8-60.50%, 95% CI] for metachronous metastases and 46.2% [35.6-59.98%, 95% CI] and 26.2% [17.4-39.36%, 95% CI] for synchronous metastases, respectively. Meanwhile, the median OS was 34.1 [26.5-49.5, 95% CI] and 60.8 [50-70.9, 95% CI] months, respectively. Thus, our study revealed statistically significant differences in OS and median OS of mRCC patients when metastasectomy was performed depending on the type of metastases ($p<0.0001$).

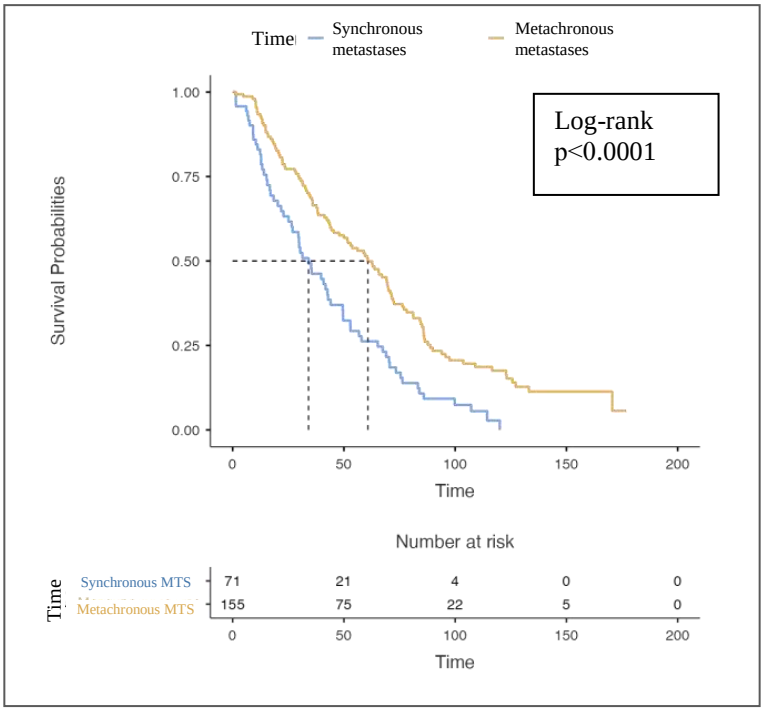


Figure 5.58 – Kaplan-Meier curves of OS indicators of mRCC patients when performing metastasectomy (N=226) depending on the type of metastases

When evaluating the mRCC patients included in the study, Table 5.59 shows that solitary metastases were detected in 35 (15.5%), single metastases in 68 (30.1%), and multiple metastases in 123 (54.4%) patients. In this subgroup, patients with multiple metastases prevailed in 54.4% of cases.

Table 5.59 – Distribution of mRCC patients undergoing metastasectomy depending on the number of metastases

Number of metastases	Number of patients	HR
Solitary	35 (15.5)	–
Single	68 (30.1)	1.02 (0.66-1.59, p=0.926)
Multiple	123 (54.4)	1.91 (1.27-2.89, p=0.002)

As can be seen from Figure 5.59, survival rates directly depend on the number of metastases. In patients with solitary, single, and multiple metastases, the 3- and 5-year OS rates at metastasectomy were 77,1% [64.4-92.39%, 95% CI] and 65.4%

[51.3-83.34%, 95% CI], 80.0% [70.9-90.38%, 95% CI] and 58.1% [47.2-71.49%, 95% CI], 43.1% [34.7-53.46%, 95% CI] and 27.5% [20.1-37.71%, 95% CI], respectively. Meanwhile, the median OS was 72.2 [60.8-85.9, 95% CI], 69.8 [53-81.1, 95% CI], and 31.3 [28-41.2, 95% CI] months, respectively.

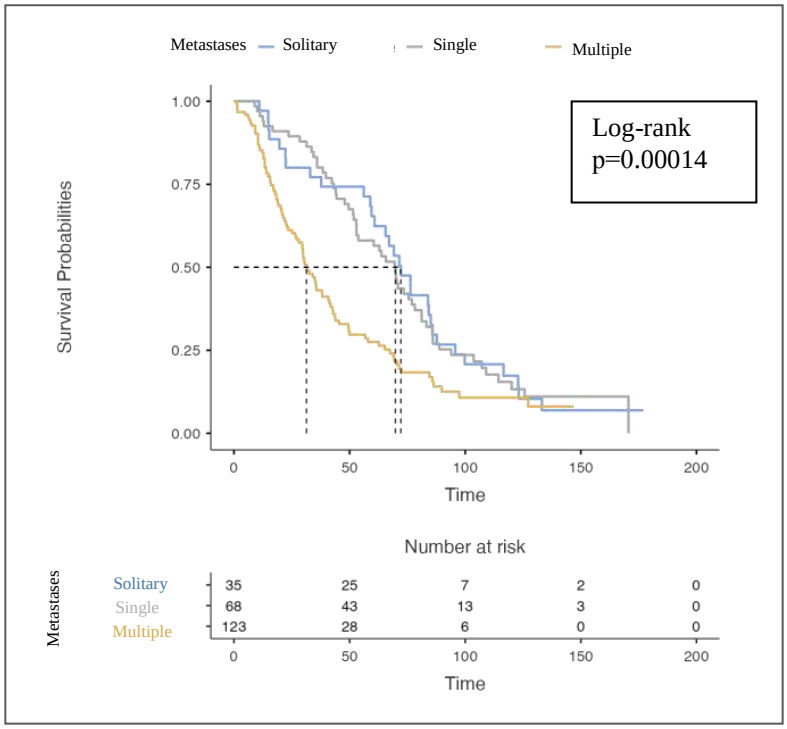


Figure 5.59 – Kaplan-Meier curves of OS indices of mRCC patients (N=226) when metastasectomy was performed depending on the amount of metastasis

Thus, the study revealed statistically significant differences in the rates of OS and median OS in mRCC patients when metastasectomy was performed depending on the number of metastases (p=0.00014).

5.4.3 Influence of laboratory parameters on the indicators of the Survival rates of patients with metastatic renal-cell carcinoma in the performance of metastasectomy

When evaluating the patients included in the study depending on the hemoglobin level were distributed as follows. Thus, normal hemoglobin level was

noted in 176 (77.9) patients and anemia was noted in 50 (22.1) patients. Thus, 77.9% of mRCC patients in our study had anemia as shown in Table 5.60.

Table 5.60 – Distribution of mRCC patients undergoing metastasectomy depending on hemoglobin level

Hemoglobin level	Number of patients	HR
Hemoglobin's normal	176 (77.9)	–
Anemia	50 (22.1)	2.07 (1.47-2.91, p<0.001)

The presented Kaplan-Meier curves (Figure 5.60) show that the 3-year and 5-year RRs for normal hemoglobin were 66.7% [59.8-74.3%, 95% CI] and 50.4% [43.2-58.8%, 95% CI], respectively, and for anemia, these values decreased significantly to 37.0% [25.4-53.9%, 95% CI] and 18.5% [10.0-34.3%, 95% CI], respectively.

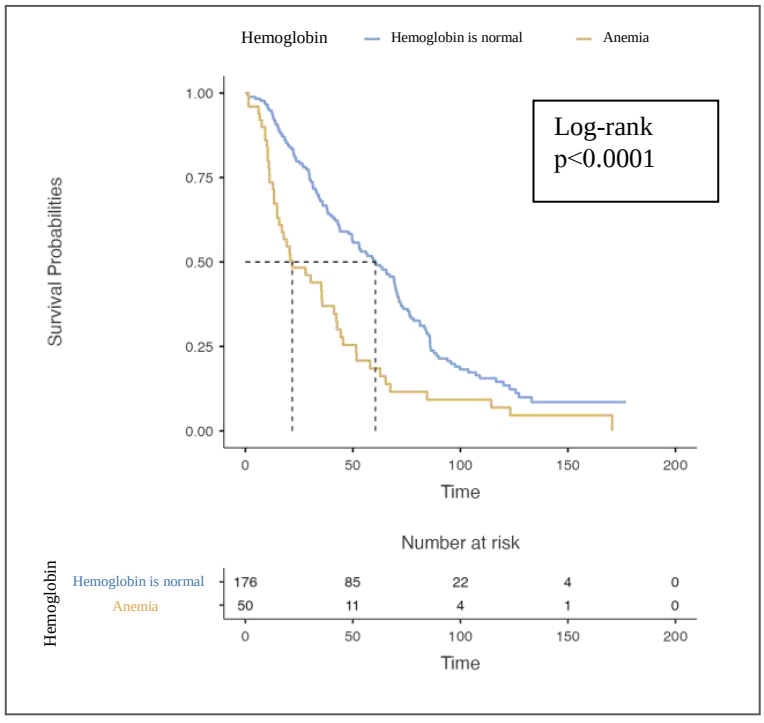


Figure 5.60 – Comparison of OS indicators of patients with mRCC (N=226) when performing metastasectomy depending on hemoglobin level

Meanwhile, the median OS also differed according to hemoglobin level and was 60.5 [49.6-70.3, 95% CI] and 21.8 [15.7-42.3, 95% CI] months, respectively. Thus, the study revealed statistically significant differences in OS and median OS depending on hemoglobin level in mRCC patients undergoing metastasectomy ($p<0.0001$).

When evaluating the patients included in the study depending on the level of alkaline phosphorus were distributed as follows. Thus, as can be seen from Table 5.61, a normal level of alkaline phosphorus was detected in 154 (68.1) patients, and elevation of this index was noted in 72 (31.9) patients. Thus, 2/3 of patients with mRCC had normal alkaline phosphate levels.

Table 5.61 – Distribution of mRCC patients undergoing metastasectomy depending on alkaline phosphate levels

Alkaline phosphatase level	Number of patients	HR
alkaline phosphorus is normal	154 (68.1)	–
alkaline phosphorus is elevated	72 (31.9)	1.47 (1.08-2.00, p=0.015)

Figure 5.61 shows that the 3-year and 5-year OS rates for normal CF were 63.7% [56.32-72.0%, 95% CI] and 48.7% [41.09-57.8%, 95% CI], respectively, When ALF was elevated, these rates decreased to 52.6% [41.88-66.1%, 95% CI] and 32.1% [22.55-45.8%, 95% CI], respectively. Meanwhile, the median OS was 59 [43.8-69.8, 95% CI] and 41.2 [33-53, 95% CI] months, respectively.

Thus, the study revealed statistically significant differences in OS and median OS depending on the level of CF in mRCC patients when metastasectomy was performed ($p=0.0014$).

When evaluating the patients included in the study depending on the level of LDH were distributed as follows. Thus, 168 (74.3%) patients had normal LDH levels, and elevation of this index was noted in 58 (25.7%) patients, as shown in Table 5.62.

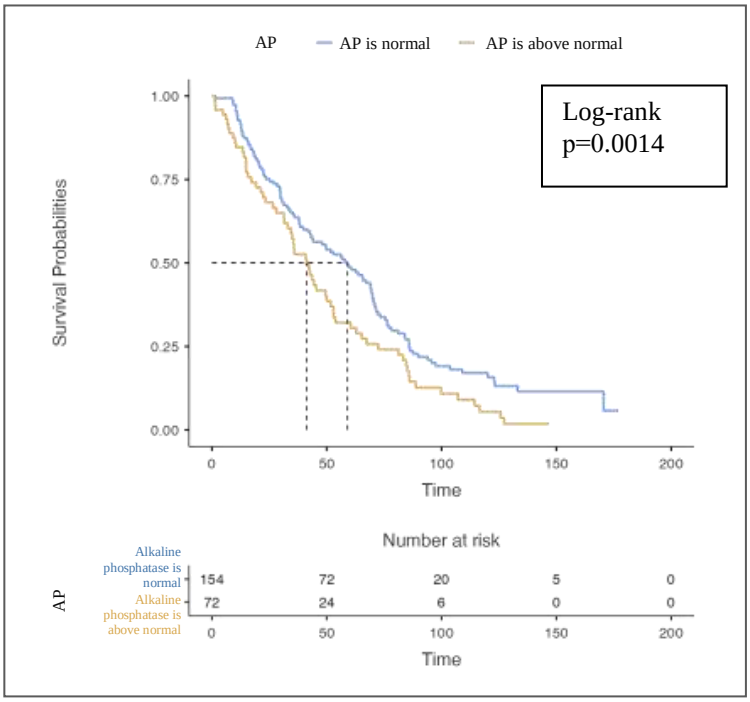


Figure 5.61 – Comparison of OS indicators of patients with mRCC (N=226) in metastasectomy depending on the level of CF

Table 5.62 – Distribution of mRCC patients undergoing metastasectomy depending on LDH level

LDH level	Number of patients	HR
LDH is normal	168 (74.3)	–
LDH is elevated	58 (25.7)	1.25 (0.90-1.73, p=0.185)

The presented Kaplan-Meier curves (Figure 5.62) show that the 3-year and 5-year OS rates for normal patients with LDH were 59.24% [52.05-67.44%, 95% CI] and 45.45% [38.17-54.11%, 95% CI], and for elevated LDH were 62.95% [51.25-77.33%, 95% CI] and 38.15% [27.06-53.79%, 95% CI], respectively. Meanwhile, the median OS was 45.4 [38.4-65.7, 95% CI] and 50 [39.8-60.8, 95% CI] months, respectively.

Thus, the conducted study showed no statistically significant differences in OS and median OS as a function of LDH level in mRCC patients undergoing mestasectomy (p=0.18).

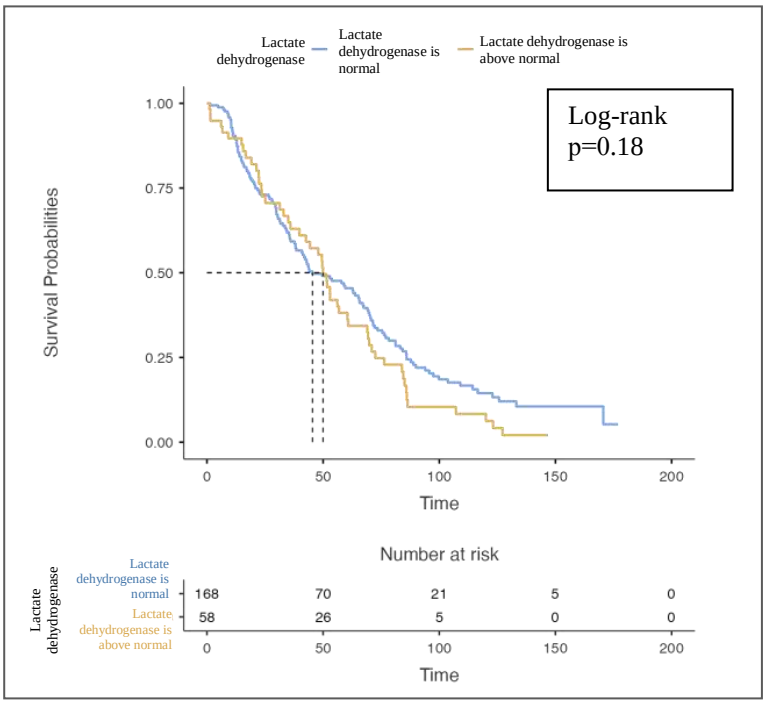


Figure 5.62 – Comparison of OS indicators of patients with mRCC (N=226) when performing metastasectomy depending on LDH levels

5.4.4 Effect of metastasis localization on indices of Survival rates of patients with metastatic renal-cell carcinoma when performing metastasectomy

The distribution of mRCC patients undergoing metastasectomy depending on the presence of bone metastases is presented in Table 5.63.

Table 5.63 – Distribution of mRCC patients undergoing metastasectomy depending on the presence of bone metastases

Bone metastasis	Number of patients	HR
Bone metastasis (-)	120 (53.1)	–
Bone metastases (+)	106 (46.9)	1.72 (1.28-2.31, p<0.001)

The presented Kaplan-Meier curves (Figure 5.63) show that the 3-year and 5-year OS rates in the absence of bone metastases were 69.1% [61.0-78.2%, 95% CI]

and 54.4% [45.8-64.7%, 95% CI], and in the presence of bone metastases were 50.0% [41.1-60.9%, 95% CI] and 31.1% [23.1-41.9%, 95% CI], respectively. Meanwhile, the median OS was 65.7 [53-71.4, 95% CI] and 38.1 [29.9-49.6, 95% CI] months, respectively. Thus, the study revealed statistically significant differences in OS and median OS in mRCC patients when metastasectomy and absence/presence of bone metastases were performed (p=0.00027).

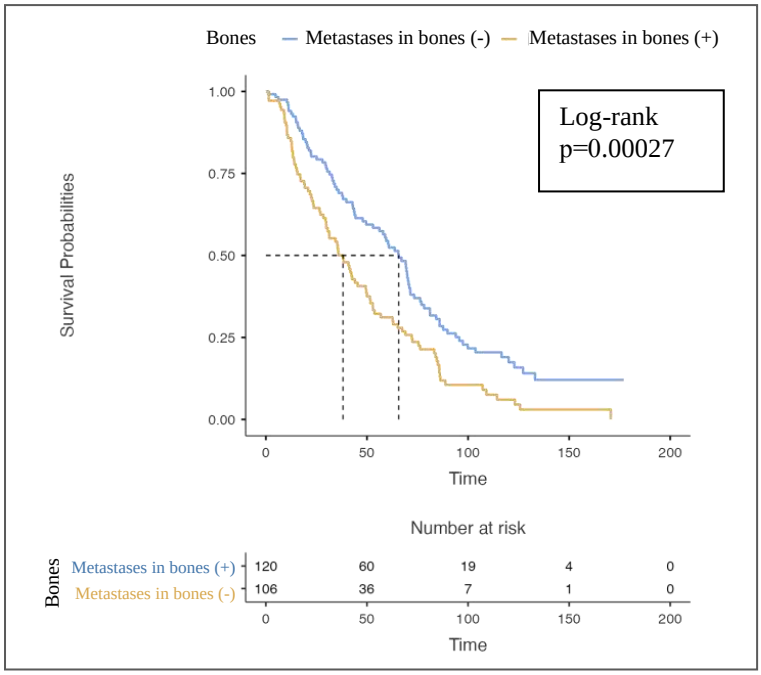


Figure 5.63 – Comparison of OS indicators of mRCC patients with absence/presence of bone metastases when performing metastasectomy (N=226)

The distribution of mRCC patients undergoing metastasectomy depending on the presence of lung metastases is presented in Table 5.64.

Table 5.64 – Distribution of mRCC patients undergoing metastasectomy depending on the presence of lung metastases

Lung metastasis	Number of patients	HR
Lung metastases (-)	99 (43.8)	–
Lung metastases (+)	127 (56.2)	1.01 (0.75-1.36, p=0.932)

The presented Kaplan-Meier curves (Figure 5.64) show that the 3-year and 5-year OS rates were 65.3% [56.38-75.6%, 95% CI] and 45.1% [36.01-56.6%, 95% CI] in the absence of lung metastases, and 56.0% [47.68-65.8%, 95% CI] and 42.1% [33.92-52.3%, 95% CI] in the presence of lung metastases, respectively. The median OS was 53 [44-69.3, 95% CI] and 43 [35.7-63.7, 95% CI] months, respectively.

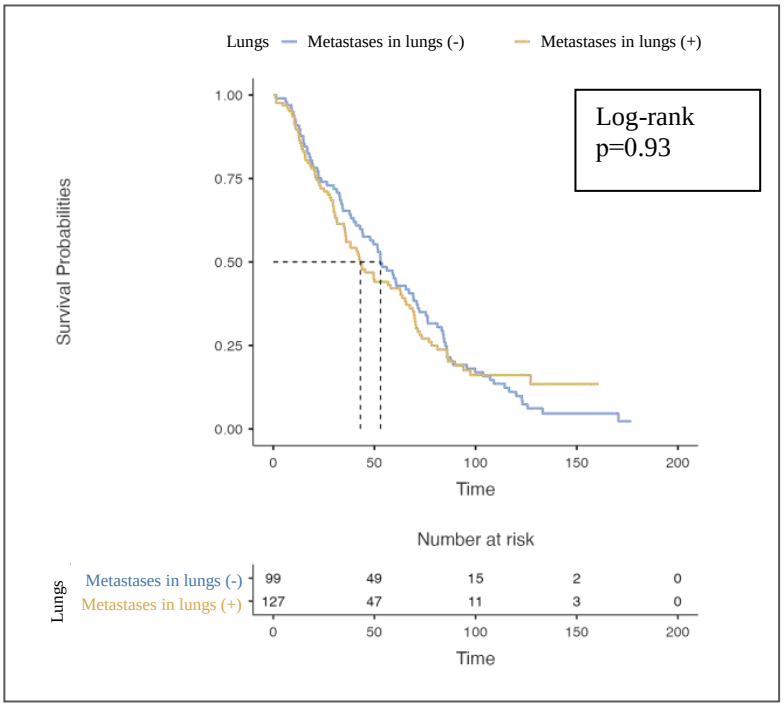


Figure 5.64 – Comparison of OS indicators of mRCC patients with absence/presence of lung metastases when performing metastasectomy (N=226)

Thus, the study did not reveal statistically significant differences in OS and median OS in mRCC patients undergoing metastasectomy and absence/presence of lung metastases (p=0.93).

The distribution of mRCC patients undergoing metastasectomy depending on the presence of lymph node metastases is presented in Table 5.65.

Table 5.65 – Distribution of mRCC patients undergoing metastasectomy depending on the presence of metastases to lymph nodes

Metastasis to Lymph nodes	Number of patients	HR
Metastases to lymph nodes (-)	174 (77.0)	–
Metastases to lymph nodes (+)	52 (23.0)	1.03 (0.71-1.48, p=0.894)

The presented Kaplan-Meier curves (Figure 5.65) show that the 3-year and 5-year OS rates in the absence of lymph node metastases were 60.7% [53.7-68.65%, 95% CI] and 44.0% [36.9-52.40%, 95% CI], and in the presence of lymph node metastases were 58.1% [45.5-74.20%, 95% CI] and 41.2% [28.9-58.68%, 95% CI], respectively. Meanwhile, the median OS was 51.5 [40.9-65.2, 95% CI] and 47.9 [34.1-70.6, 95% CI] months, respectively.

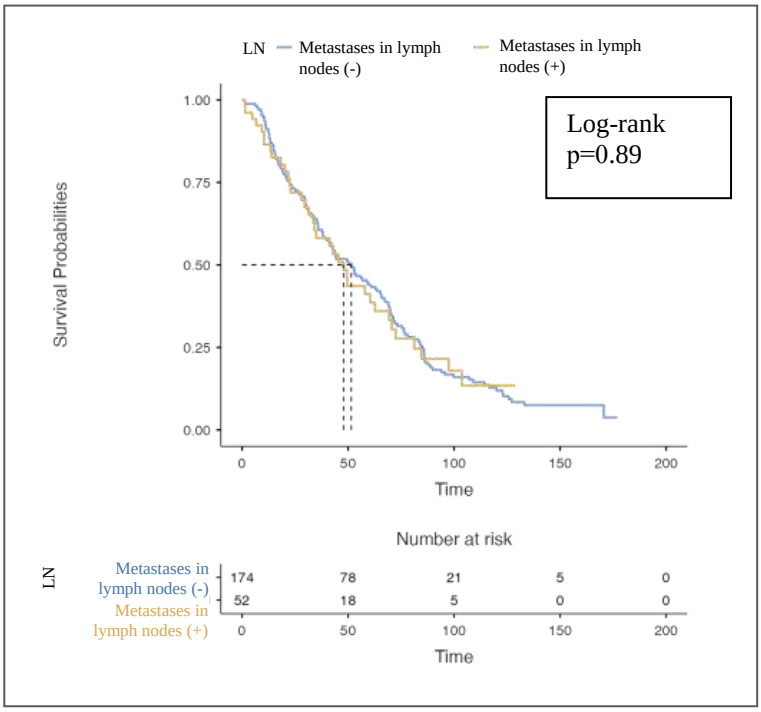


Figure 5.65 – Comparison of OS indicators of mRCC patients with absence/presence of metastases to lymph nodes when performing metastasectomy (N=226)

Thus, the study revealed no statistically significant differences in the OS and median OS in mRCC patients when metastasectomy was performed in the absence/absence of metastases to lymph nodes (p=0.89).

The distribution of mRCC patients undergoing metastasectomy depending on the presence of liver metastases is presented in Table 5.66.

Table 5.66 – Distribution of mRCC patients undergoing metastasectomy depending on the presence of liver metastases

Metastasis to the liver	Number of patients	HR
Metastasis to the liver (-)	205 (90.7)	–
Metastasis to the liver (+)	21 (9.3)	0.80 (0.48-1.33, p=0.385)

The presented Kaplan-Meier curves (Figure 5.66) show that the 3-year and 5-year OS rates were 58.9% [52.3-66.4%, 95% CI] and 42.1% [35.5-49.9%, 95% CI] in the absence of liver metastases, and 71.1% [54.0-93.6%, 95% CI] and 55.0% [36.9-82.2%, 95% CI] in the presence of liver metastases, respectively. The median OS was 47.9 [39.8-59.5, 95% CI] and 65.2 [44.3-127.2, 95% CI] months, respectively.

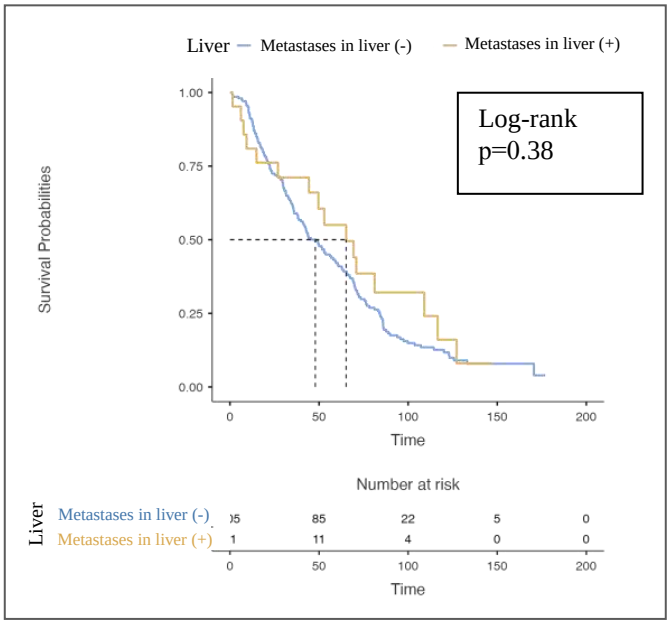


Figure 5.66 – Comparison of OS indicators of mRCC patients with absence/presence of liver metastases when performing metastasectomy (N=226)

Thus, the study did not reveal statistically significant differences in OS and median OS in mRCC patients when metastasectomy was performed in the absence/ presence of liver metastases (p=0.38).

The distribution of mRCC patients undergoing metastasectomy depending on the presence of brain metastases is presented in Table 5.67.

Table 5.67 – Distribution of mRCC patients undergoing metastasectomy depending on the presence of brain metastases

Metastasis to the brain	Number of patients	HR
Metastasis to the brain (-)	203 (89.8)	–
Metastases to the brain (+)	23 (10.2)	1.46 (0.92-2.33, p=0.110)

The presented Kaplan-Meier curves (Figure 5.67) show that the 3-year and 5-year OS rates were 61.7% [55.1-69.0%, 95% CI] and 45.3% [38.7-53.2%, 95% CI] in the absence of brain metastases, and 47.4% [30.7-73.2%, 95% CI] and 26.4% [12.7-54.6%, 95% CI] in the presence of brain metastases, respectively. Meanwhile, the median OS was 51.7 [42.9-65.2, 95% CI] and 35.5 [18.4-86.3, 95% CI] months, respectively. Thus, the study revealed no statistically significant differences in OS and median OS in mRCC patients undergoing metastasectomy in the absence/presence of brain metastases (p=0.11).

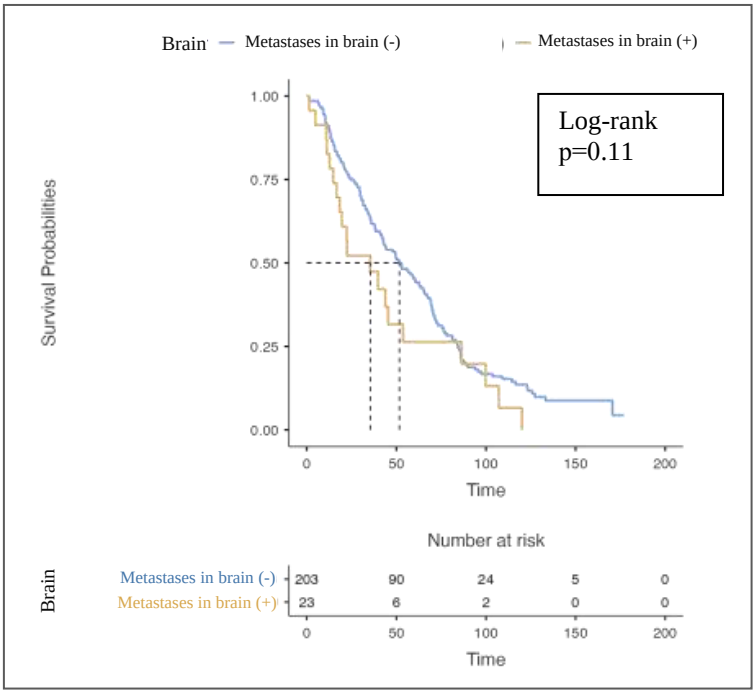


Figure 5.67 – Comparison of OS indicators of mRCC patients with absence/presence of brain metastases when performing metastasectomy (N=226)

The distribution of mRCC patients undergoing metastasectomy depending on the volume of surgery is presented in Table 5.68.

Table 5.68 – Distribution of mRCC patients undergoing metastasectomy depending on the volume of surgery

Metastasectomy volume	Number of patients	HR
Incomplete metastasectomy	120 (53.1)	–
Complete metastasectomy	106 (46.9)	0.17 (0.12-0.24, p<0.001)

The presented Kaplan-Meier curves (Figure 5.68) show that the 3-year and 5-year OS rates for complete metastasectomy were 89.5% [83.9-95.6%, 95% CI] and 71.2% [63.0-80.5%, 95% CI], and 30.6% [22.9-41.1%, 95% CI] and 13.8% [8.1-23.4%, 95% CI] for incomplete metastasectomy, respectively. Meanwhile, the median OS also differed and was 76.9 [70.3-86, 95% CI] and 28.4 [20.3-33.5, 95% CI] months, respectively.

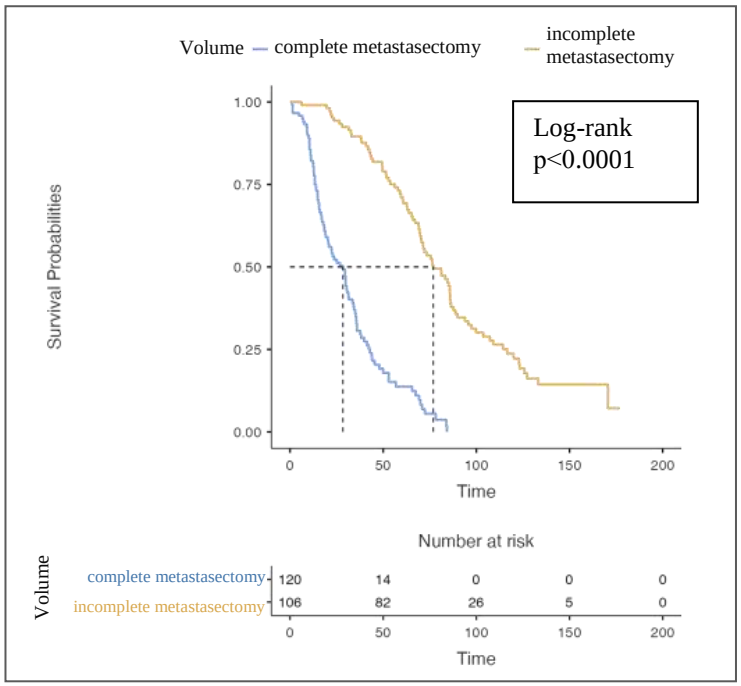


Figure 5.68 – Comparison of OS indices of mRCC patients undergoing metastasectomy (N=226) depending on the volume of cytoreductive surgery

Thus, the study revealed statistically significant differences in OS and median OS in mRCC patients when complete metastasectomy was performed (p<0.0001).

The distribution of mRCC patients undergoing metastasectomy depending on whether the surgery was performed before or after initiation of systemic therapy is summarized in Table 5.69.

Table 5.69 – Distribution of mRCC patients undergoing metastasectomy, depending on whether the surgery was performed before or after the start of systemic therapy

Metastasectomy	Number of patients	HR
Before starting systemic therapy	128 (56.9)	–
After starting systemic therapy	97 (43.1)	0.35 (0.25-0.47, p<0.001)

The presented Kaplan-Meier curves (Figure 5.69) show that the 3-year and 5-year ORs of performing metastasectomy before the initiation of systemic therapy were 42.7% [34.5-52.9%, 95% CI] and 22.6% [15.8-32.3%, 95% CI], and those of performing metastasectomy after the initiation of systemic therapy were 81.2% [73.7-89.4%, 95% CI] and 67.3% [58.5-77.4%, 95% CI], respectively. However, the median OS also differed and was 31.5 [25.1-40.9, 95% CI] and 73.4 [69.5-85.9, 95% CI] months, respectively.

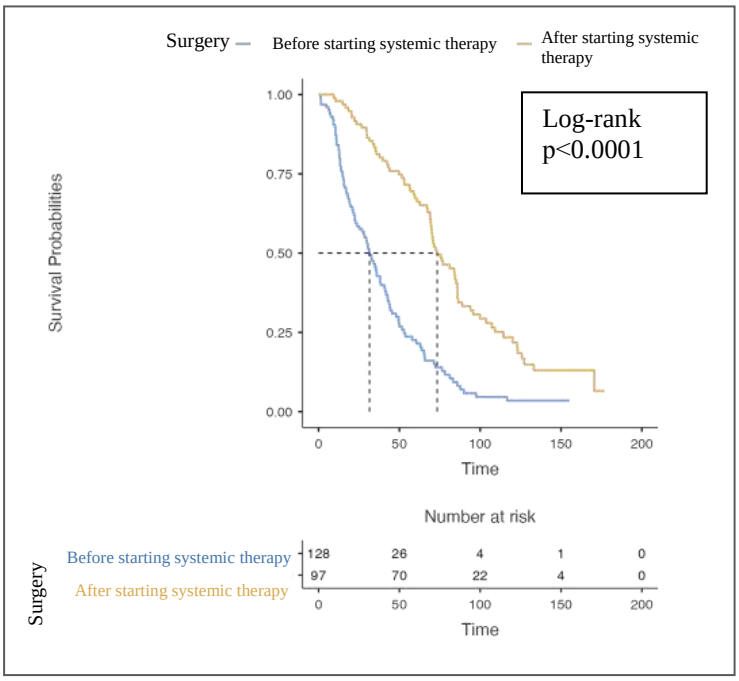


Figure 5.69 – Comparison of OS rates of mRCC patients undergoing metastasectomy (N=226) before or after initiation of systemic therapy

Thus, the conducted study revealed statistically significant differences in OS and median OS in mRCC patients at metastasectomy after initiation of systemic therapy ($p<0.0001$).

The presented table 5.70 shows that in a single-factor analysis, tumor differentiation, number and type of metastases, ECOG status, presence of bone metastases, hemoglobin, alkaline phosphatase and ESR levels, NE, complete metastasectomy, and metastasectomy before systemic therapy were factors affecting RRs in metastasectomized mRCC patients. In multivariate analysis, ECOG status, tumor differentiation degree, NE and radiation therapy, complete metastasectomy and metastasectomy prior to systemic therapy were the factors influencing OS in mRCC patients.

Table 5.70 – Cox proportional hazards model of the effect on OS rates in the group of mRCC patients who underwent metastasectomy (N=226)

Factors	Gradations	N (patients)	HR (single-factor)	HR (multivariate)
Gender	men	143 (63.3)	–	–
	women	83 (36.7)	0.87 (0.64-1.19, p=0.381)	0.94 (0.66-1.34, p=0.738)
Age	18-44	16 (7.1)	–	–
	45-59	104 (46.0)	0.64 (0.37-1.11, p=0.112)	0.70 (0.37-1.31, p=0.259)
	60-74	95 (42.0)	0.68 (0.39-1.19, p=0.177)	0.60 (0.32-1.13, p=0.113)
	over 75	11 (4.9)	1.14 (0.51-2.55, p=0.741)	1.76 (0.69-4.53, p=0.238)
Localization of the primary kidney tumors	on the right	121 (53.5)	–	–
	on the left	100 (44.2)	0.90 (0.66-1.21, p=0.465)	0.98 (0.70-1.36, p=0.895)
	bilateral	5 (2.2)	0.62 (0.20-1.97, p=0.421)	0.67 (0.19-2.32, p=0.528)

Continuation of Table 5.70

Factors	Gradations	N (patients)	HR (single-factor)	HR (multivariate)
ECOG status	ECOG0	16 (7.1)	–	–
	ECOG1	97 (42.9)	0.95 (0.51-1.77, p=0.878)	0.88 (0.43-1.81, p=0.737)
	ECOG2	81 (35.8)	2.09 (1.13-3.86, p=0.019)	1.61 (0.77-3.38, p=0.206)
	ECOG3	32 (14.2)	6.88 (3.44-13.76, p<0.001)	3.76 (1.59-8.87, p=0.002)
CN	CN (+)	216 (95.6)	–	–
	CN (-).	10 (4.4)	4.54 (1.94-10.64, p<0.001)	5.42 (2.07-14.21, p=0.001)
Histological variant	Clear-cell	213 (94.2)	–	–
	Non- clear-cell	13 (5.8)	1.15 (0.61-2.19, p=0.659)	0.56 (0.27-1.17, p=0.124)
Differentiation tumors by Fuhrman	1	61 (27.0)	–	–
	2	88 (38.9)	2.24 (1.52-3.30, p<0.001)	1.80 (1.12-2.91, p=0.016)
	3	77 (34.1)	3.19 (2.17-4.70, p<0.001)	1.98 (1.14-3.42, p=0.015)
Type of metastasis	synchronous	71 (31.4)	–	–
	metachronous	155 (68.6)	0.52 (0.38-0.71, p<0.001)	1.32 (0.85-2.05, p=0.214)
Number of metastases	solitary	35 (15.5)	–	–
	single	68 (30.1)	1.02 (0.66-1.59, p=0.926)	0.95 (0.56-1.61, p=0.850)
	multiple	123 (54.4)	1.91 (1.27-2.89, p=0.002)	1.68 (0.86-3.29, p=0.131)
Bones	bone metastases (-)	120 (53.1)	–	–
	bone metastases (+)	106 (46.9)	1.72 (1.28-2.31, p<0.001)	0.86 (0.55-1.35, p=0.517)
Lungs	lung metastases (-)	99 (43.8)	–	–
	lung metastases (+)	127 (56.2)	1.01 (0.75-1.36, p=0.932)	0.76 (0.50-1.17, p=0.216)

Continuation of Table 5.70

Factors	Gradations	N (patients)	HR (single-factor)	HR (multivariate)
Liver	liver metastases (-)	205 (90.7)	–	–
	liver metastases (+)	21 (9.3)	0.80 (0.48-1.33, p=0.385)	0.57 (0.29-1.10, p=0.094)
Lymph nodes	lymph nodes metastases (-)	174 (77.0)	–	–
	lymph nodes metastases (+)	52 (23.0)	1.03 (0.71-1.48, p=0.894)	0.71 (0.45-1.13, p=0.148)
Brain	brain metastases (-)	203 (89.8)	–	–
	brain metastases (+)	23 (10.2)	1.46 (0.92-2.33, p=0.110)	1.47 (0.84-2.58, p=0.178)
Hemoglobin	hemoglobin is normal	176 (77.9)	–	–
	anemia	50 (22.1)	2.07 (1.47-2.91, p<0.001)	1.20 (0.79-1.83, p=0.394)
Alkaline phosphatase	alkaline phosphorus is normal	154 (68.1)	–	–
	alkaline phosphorus is elevated	72 (31.9)	1.47 (1.08-2.00, p=0.015)	1.07 (0.72-1.58, p=0.751)
LDH	LDH is normal	168 (74.3)	–	–
	LDH is elevated	58 (25.7)	1.25 (0.90-1.73, p=0.185)	1.08 (0.74-1.57, p=0.700)
ESR	ESR's normal	85 (37.6)	–	–
	ESR's elevated	141 (62.4)	1.90 (1.39-2.60, p<0.001)	1.43 (0.91-2.24, p=0.119)
Platelets	platelets normally	171 (75.7)	–	–
	thrombocytosis	26 (11.5)	1.24 (0.79-1.94, p=0.359)	1.34 (0.77-2.33, p=0.306)
	thrombocytopenia	29 (12.8)	1.27 (0.84-1.93, p=0.262)	1.11 (0.66-1.87, p=0.704)

Continuation of Table 5.70

Factors	Gradations	N (patients)	HR (single-factor)	HR (multivariate)
Metastasectomy	incomplete	119 (52.9)	–	–
	complete	106 (47.1)	0.17 (0.12-0.24, p<0.001)	0.16 (0.10-0.25, p<0.001
	after starting systemic therapy	128 (56.9)	–	–
	prior to systemic therapy	97 (43.1)	0.35 (0.25-0.47, p<0.001)	0.36 (0.24-0.52, p<0.001)
The drug in line 1	TKI	221 (97.8)	–	–
	ICI	5 (2.2)	0.00 (0.00-Inf, p=0.993)	0.00 (0.00-Inf, p=0.994)
Radiation therapy	radiation therapy (-)	171 (75.7)	–	–
	radiation therapy (+)	55 (24.3)	0.91 (0.65-1.29, p=0.612)	0.61 (0.41-0.91, p=0.015)

In conclusion, we created 2 general tables of prognostic factors in single – multivariate analysis affecting survival rates in mRCC patients under different cytoreductive surgical interventions (Tables 5.71, 5.72).

Table 5.71 – Single-factor analysis of prognostic factors affecting survival rates in mRCC patients undergoing cytoreductive surgery

Signs	CN (+)	Metastasectomy	CN+Metastasectomy	CN (-)
Histologic variant	**(+)**			
Degree of differentiation	**(+)**	**(+)**		**(+)**
ECOG status	**(+)**	**(+)**	**(+)**	**(+)**
Number metastases	**(+)**	**(+)**	**(+)**	
Hemoglobin	**(+)**	**(+)**	**(+)**	**(+)**

Continuation of Table 5.71

Signs	CN (+)	Metastasectomy	CN+Metastasectomy	CN (-)
CF	**(+)**	**(+)**		
LDH	**(+)**			
Metatstases in the bone		**(+)**		
Metastasis to the liver	**(+)**			
Metastasis into the brain				**(+)**

Thus, Table 5.71 shows that the greatest number of additional factors that should be taken into account when choosing cytoreductive interventions was found in patients before CN and metastasectomy. It was also noted that most prognostic factors for CN (+) and (-) were similar, except for alkaline phosphate, LDH, bone, liver, and brain metastases.

Table 5.72 – Multivariate analysis of prognostic factors affecting survival rates in patients with mRCC undergoing cytoreductive surgery

Signs	CN (+)	Metastasectomy	CN+Metastasectomy	CN (-)
Gender				**(+)**
Age	**(+)**		**(+)**	
Histologic variant			**(+)**	
Degree of differentiation	**(+)**	**(+)**		**(+)**
ECOG status	**(+)**	**(+)**	**(+)**	**(+)**
Number metastases	**(+)**		**(+)**	
Bone metastasis	**(+)**		**(+)**	
Hemoglobin	**(+)**			

Thus, Table 5.72 shows that the greatest number of additional factors that should be paid attention to when choosing cytoreductive interventions was revealed in patients before performing CN and a combination of CN and metastasectomy. At the same time all additional prognostic factors influencing the survival rates of mRCC patients are practically similar in these cytoreductive surgeries, the most important factors were ECOG status and tumor differentiation degree.

Conclusion

The successes of modern systemic therapy have questioned the necessity of surgical treatment of the primary tumor and metastases in mRCC patients. Our study shows that, for the most part, clinical and morphological characteristics of the tumor and metastatic disease itself influence the prognosis of patients and the nature of cytoreductive surgeries. In our study, we investigated the effect of different cytoreductive treatments on the OS indices of mRCC patients. We studied the effect of cytoreductive nephrectomy, mestasectomy, their combinations, and no CN under different prognostic factors and their impact on survival rates. A single- and multivariate analysis was performed in this category to identify additional factors influencing the choice of a particular cytoreductive intervention method in mRCC patients.

First, we analyzed 330 patients with mRCC who underwent CN. In single-factor analysis in patients who underwent CN, histological variant and tumor differentiation degree according to Fuhrman, number of metastases, ECOG status, presence of liver metastases, as well as hemoglobin, alkaline phosphatase and LDH levels were the factors influencing the OS in mRCC patients undergoing CN. In multivariate analysis, age (45-59 and 60-74 years old), Fuhrman tumor differentiation degree, number of metastases, ECOG status, bone metastases and hemoglobin level were additional factors influencing the OS in mRCC patients.

Next, we examined prognostic factors affecting survival in 62 mRCC patients who underwent CN and metastasectomy. In single-factor analysis, ECOG status, number of metastases, and hemoglobin level were the factors influencing survival

rates in mRCC patients. In multivariate analysis, age (older than 75 years), histologic type, ECOG status, number of metastases, and bone metastases were additional prognostic factors affecting OS in mRCC patients who underwent cytoreductive nephrectomy and metastasectomy.

We also studied prognostic factors influencing survival rates in 73 patients with mRCC who did not undergo CN. In a single-factor analysis, the degree of tumor differentiation according to Fuhrman, ECOG status and the presence of brain metastases, hemoglobin and platelet levels were the factors affecting survival rates. In multivariate ECOG status and brain metastases were additional factors influencing the OS in patients who did not undergo CN.

It was noted that in single-factor analysis most prognostic factors in CN (+) and (-) were similar, except for alkaline phosphate, LDH, bone, liver and brain metastases. The multivariate analysis revealed a greater number of prognostic factors affecting the RI in the group of patients with CN.

The study of the influence of prognostic factors on OS indices in 226 patients with mRCC who underwent metastasectomy was carried out. In single-factor analysis, the degree of tumor differentiation, the number and type of metastases, ECOG status, the presence of bone metastases, as well as the level of hemoglobin, alkaline phosphatase and sedimentation rate, performing CN, performing complete metastasectomy and performing metastasectomy before systemic therapy were the factors influencing the OS in metastasectomized mRCC patients. In multivariate analysis, ECOG status, tumor differentiation degree, CN and radiation therapy, complete metastasectomy and metastasectomy prior to systemic therapy were the factors influencing OS in mRCC patients.

Thus, in our study, the highest number of additional factors of mRCC patients that should be paid attention to was found in patients before performing CN and combination of CN and metastasectomy.

Historically, previous studies have shown that CN should be performed unequivocally in all patients with mRCC. Further studies have questioned whether CN should be performed. We examined prognostic factors and concluded that the

IMDC model is currently insufficient for selecting patients for cytoreductive surgery. Based on our study, we believe that additional prognostic factors that influence the choice of cytoreductive interventions in patients with mRCC are the degree of tumor differentiation, type and number of metastases, as well as the presence of bone, lung, and brain metastases.

Chapter 6
ANALYSIS OF RESULTS OF SYSTEMIC THERAPY FOR METASTATIC RENAL CELL CANCER

Since the beginning of the 21st century, tremendous progress has been made in the treatment of mRCC. Understanding the molecular profile of tumor cells has led to the development of systemic therapies, and the study of antitumor immunity has changed the clinical presentation of the disease. The paradigm has changed twice in the last decade, improving patient outcomes by using combination regimens with ICI and TKI (axitinib plus pembrolizumab or avelumab) [248, 266].

Such drug combinations are now approved and are part of an ever-expanding therapeutic armamentarium. Nevertheless, this has created a need to discover predictors and prognostic biomarkers that can personalize patient treatment to improve efficacy and reduce toxicity of therapy.

Systemic therapy was given to 981 patients, of whom 667 (68.0%) received 2 lines and 348 (35.5%) received three lines of systemic therapy. The number of patients in line 4 was 138 (14.1%), 49 (5%) in line 5, and 23 (2.3%) patients in line 6.

6.1 Characterization of systemic therapy in lines 1-6 and its efficacy in patients with metastatic renal cell cancer

We analyzed the outcome of therapy by lines depending on the type of systemic therapy and histological characteristics of the tumor. During the 1st line therapy we analyzed patients with single, solitary, multiple metastases taking into account the number of affected organs. The outcomes were conditionally divided into favorable, including all cases of complete response, partial response and stabilization, and unfavorable – progression, death or deregistration.

6.1.1 Characterization and efficiency of the 1st line systemic therapy in patients with metastatic renal cell cancer

In the first line, all 981 mRCC patients received various types of systemic treatment. The distribution of patients by main groups of drugs is presented in Table 6.1.

Table 6.1 – Distribution of patients according to 1st line drug group

The drug	Number of patients	%
Chemotherapy	6	0.5
TKI	774	79.0
Cytokines	167	17.0
ICI	34	3.5
TOTAL	981	100.0

The overall response to treatment in the 1st line of systemic therapy was 9.5%. Complete response was registered in only 1% of patients, partial response in 8.5%, stabilization in 42.4%, and progression in 39.8% of patients (Table 6.2).

Table 6.2 – Distribution of treatment response options in the 1st line of systemic therapy

Response to therapy	%	Number of patients
Complete response	1.0	10
Partial response	8.5	83
Stabilization	42.4	416
Progression	39.8	391
Withdrawn	3.6	35
Death	4.7	46
Total	100	981

Taking into account the previously obtained data on survival rates of patients with solitary, single and multiple metastases of RCC, the results of the 1st line of systemic therapy were analyzed taking into account the division into these subgroups.

Table 6.3 shows that the frequency of outcomes in the 1st line differed: complete response and deregistration were more frequent in patients with solitary metastases, stabilization was more frequent in single metastases, partial response and fatal outcome were more frequent in multiple metastases.

Table 6.3 – Frequency of outcomes of 1st line systemic therapy in patients with solitary, single and multiple RCC metastases *(χ^2=123.707, df=20, p=.000000)*

Outcome of 1st line of therapy	Solitary metastases	Single metastases	Multiple metastases
Complete response	3 (3.33%)	4 (1.59%)	3 (0.47%)
Partial response	4 (4.44%)	19 (7.54%)	60 (9.39%)
Stabilization	44 (48.89%)	129 (51.19%)	243 (38.03%)
Progression	33 (36.67%)	85 (33.73%)	273 (42.72%)
Dismissed	5 (5.56%)	10 (3.97%)	20 (3.13%)
Death	1 (1.11%)	5 (1.98%)	40 (6.26%)

Considering these data, we analyzed the outcome rates according to drug group, which revealed statistically significant differences only in patients with multiple RCC metastases (Table 6.3), while patients with solitary and single metastases did not differ in outcome rates (χ^2=3.59439, df=20, p=.463672 andχ^2=28.9532, df=20, p=.088684, respectively).

Table 6.4 shows that patients with multiple RCC metastases who received ICI had a partial response more often (almost half of cases).

Stabilization and progression of the disease were observed almost equally (in about a quarter of cases), only two patients had a fatal outcome. The percentage of mortality with TKI was approximately the same. The most frequent outcome of first-line TKI was process stabilization (40.72% of cases) and progression (38.72%), with complete response and partial response being rare.

Table 6.4 – Frequency of outcomes according to 1st line treatment in patients with multiple RCC metastases *(χ^2=89.6871, df=19, p=.000000)*

The drug	Complete response	Partial response	Stabilization	Progression	Withdrawn off the books	Death
Chemotherapy	0	0	0	2 (100.0%)	0	0
TKI	3 (0.56%)	46 (9.15%)	207 (38.7%)	215 (40.2%)	26 (4.86%)	38 (7.10%)
ICI	0	14 (45.16%)	7 (22.58%)	8 (25.81%)	0	2 (6.45%)
Cytokines	0	0	29 (37.18%)	48 (61.54%)	1 (1.28%)	0

Administration of cytokines resulted in disease progression in 61.3% of patients, while stabilization occurred in 37.18% of patients. Complete or partial response and lethal outcome were not observed in any of the patients.

In patients with multiple metastases of RCC, statistically significant differences of conditionally favorable and unfavorable outcomes were revealed depending on the number of affected organs and the drug (Table 6.5). In patients with solitary and single metastases of RCC, no such dependence was observed due to the frequent involvement of a single organ. Changes of 2 or 3 organs were rare in patients with solitary metastases of RCC.

Table 6.5 – Frequency of outcomes in patients with multiple metastases of RCC according to drug group and number of organs affected *(χ^2=67.1977, df=28, p=.000176)*

The drug	Favorable outcome	Unfavorable outcome	Number of organs affected
CHEMOTHERAPY	0 (0.00%)	1 (100.00%)	1
TKI	50 (50.5%)	49 (49.5%)	
ICI	6 (66.67%)	3 (33.33%)	
Cytokines	5 (26.32%)	14 (73.68%)	

Continuation of Table 6.5

The drug	Favorable outcome	Unfavorable outcome	Number of organs affected
CHEMOTHERAPY	0	0	2
TKI	107 (54.6%)	89 (45.4%)	
ICI	4 (57.14%)	3 (42.86%)	
Cytokines	19 (47.50%)	21 (52.50%)	
CHEMOTHERAPY	0	0	3
TKI	64 (42.76%)	86 (57.24%)	
ICI	7 (60.0%)	3 (30.00%)	
Cytokines	4 (23.53%)	13 (76.47%)	
CHEMOTHERAPY	0	1 (100.0%)	4
TKI	36 (44.4%)	47 (56.6%)	
ICI	3 (60.0%)	2 (40.00%)	
Cytokines	1 (50.00%)	1 (50.00%)	

Table 6.5 shows that regardless of the number of organs affected, the rate of favorable outcome was higher with TKI than with other treatment options, reaching 60% on average, slightly higher with a single organ affected, 66.7%. Application of TKI resulted in unfavorable or favorable outcome with approximately 50/50 frequency, but favorable outcomes were slightly more frequent in patients with 1 or 2 organs affected than 3 or 4. The use of cytokines in 1 or 3 organ lesions resulted in a favorable outcome in half of the cases, while in 2 or 4 organ lesions a favorable outcome was observed in only a quarter of patients. Chemotherapy was administered to 2 patients, and both had unfavorable outcomes.

Depending on the drug, the treatment outcome (favorable to unfavorable) in mRCC patients was studied based on the histological characteristics of the tumor (Table 6.6).

Table 6.6 – Frequency of outcomes in 1st line systemic therapy depending on drug and histologic variant of RCC

The drug		Solitary metastases		Single metastases		Multiple metastases	
		favorable outcome	unfavorable outcome	favorable outcome	unfavorable outcome	favorable outcome	unfavorable outcome
Light-cell variant	CHEMOTHERAPY	1 (100%)	0	0	2 (100%)	0	1 (100%)
	TKI	32 (60.3%)	21 (39.6%)	110 (67.1%)	54 (32.9%)	231 (54.1%)	204 (46.9%)
	ICI	1 (100%)	0	2 (100%)	0	8 (72.73%)	3 (27.27%)
	Cytokines	11 (45.8%)	13 (54.2%)	28 (47.5%)	31 (52.5%)	28 (41.2%)	40 (58.8%)
Non-small cell variant	CHEMOTHERAPY	0	0	0	0	0	1 (100%)
	TKI	6 (85.7%)	1 (14.3%)	7 (53.9%)	6 (46.1%)	24 (32.4%)	50 (67.6%)
	ICI	0	0	0	0	1 (100.00%)	0
	Cytokines	0	1 (100%)	2 (50.00%)	2 (50.00%)	1 (10.00%)	9 (90.00%)
		χ^2=21.8495, df=11, p=0.057739		χ^2=22.1159, df=11, p=0.053592		χ^2=60.0360, df=11, p=0.000000	

Table 6.6 shows that the frequency of favorable and unfavorable outcomes in patients with mRCC differed depending on the histological type and drug in patients with multiple metastases and had no differences in patients with solitary and single metastases. Administration of TKI in the 1st line ended with a favorable outcome

in 72.73% of patients with luminal RCC and in the only patient with non-small cell cancer who received TKI. Administration of TKI in 54.1% of the patients with non-small cell variant ended with a favorable outcome, while in non-small cell tumor variants it was observed in only 32.4% of patients. The use of cytokines in patients with multiple metastases of RCC in the 1st line was effective in about half of cases in clear-cell tumor variants and only in 10% in non-small-cell variants. In clear-cell tumor variants the use of TKI was more often accompanied by favorable outcome in single metastases of RCC in 67,1% of patients. TKI therapy in 1 patient with solitary metastases and 2 patients with single metastases of RCC resulted in favorable outcome, in patients with multiple metastases, of which there were 11, favorable outcome was observed in 72,7%. The frequency of favorable and poor outcomes with cytokine administration was approximately 50/50 regardless of the number of metastases.

In patients with non-small cell variants of RCC, TKI treatment for solitary metastases was almost always accompanied by a favorable outcome, in case of single metastases the frequency of favorable outcome was higher than in case of multiple metastases of RCC (53.9% vs. 32.4%). ICI was used with favorable effect in only one patient with multiple metastases. The use of cytokines was associated with an unfavorable outcome in almost all patients with non-small cell variants of RCC with solitary and multiple metastases and 50% of cases with single metastases.

Comparison of the frequency of outcomes depending on the degree of differentiation and the group of drugs used in mRCC patients revealed that the frequency of favorable and unfavorable outcomes differed in multiple metastases and had no significant differences in solitary and single metastases (Table 6.7).

In patients with multiple G1 metastases, TKI were most frequently used in the 1st line of therapy, with a favorable outcome in 66.0%. With decreasing degree of differentiation the frequency of favorable outcome decreased to 41.2% at G3. ICI in all patients with G1 had a favorable outcome. At G2 only in 50% of patients, and at G3 in 70% of patients. Systemic cytokine therapy in patients with multiple metastases of RCC was most effective at G1, further the efficacy decreased synchronously with the decrease of tumor differentiation degree.

Table 6.7 – Frequency of outcomes in 1st line systemic therapy depending on the drug administered and the grade of differentiation of RCC

Solitary				Single				Multiple			
Grade	drug	favorable outcome	unfavorable outcome	Grade	drug	favorable outcome	unfavorable outcome	Grade	drug	favorable outcome	unfavorable outcome
1	CHEMOTHERAPY	1 (100.0%)	0	1	CHEMOTHERAPY	0	1 (100.0%)	1	CHEMOTHERAPY	0	0
1	TKI	15 (75.0%)	5 (25.0%)	1	TKI	41 (66.1%)	21 (33.9%)	1	TKI	31 (66.0%)	16 (34.0%)
1	ICI	0	0	1	ICI	0	0	1	ICI	2 (100.00%)	0
1	Cytokines	8 (50.00%)	8 (50.00%)	1	Cytokines	12 (46.15%)	14 (53.85%)	1	Cytokines	7 (70.00%)	3 (30.00%)
2	CHEMOTHERAPY	0	0	2	CHEMOTHERAPY	0	1 100.00%	2	CHEMOTHERAPY	0	0
2	TKI	20 (63.5%)	12 (37.5%)	2	TKI	47 (63.5%)	27 (36.5%)	2	TKI	106 (56.4%)	82 (43.6%)
2	ICI	0	0	2	ICI	0	0	2	ICI	6 (50.00%)	6 (50.00%)
2	Cytokines	1(20.00%)	4 (80.00%)	2	Cytokines	10 (52.63%)	9 (47.37%)	2	Cytokines	13 (44.83%)	16 (55.17%)
3	CHEMOTHERAPY	0	0	3	CHEMOTHERAPY	0	0	3	CHEMOTHERAPY	0	2 (100%)
3	TKI	3 (27.27%)	8 (72.73%)	3	TKI	30 (64.8%)	17 (36.3%)	3	TKI	120 (41.2%)	171 (58.8%)
3	ICI	1 100.00%	0	3	ICI	2 (100.00%	0	3	ICI	12 (70.59%)	5 (29.41%)
3	Cytokines	2 50.00%	2 50.00%	3	Cytokines	9 (47.37%)	10 (52.63%)	3	Cytokines	9 (23.08%)	30 (76.92%)
Chi-square: 31.7155, df=19, p=.082378				*Chi-square: 26.6833, df=19, p=.223503*				*Chi-square: 62.2787, df=19, p=.000721*			

Comparing the results of 1st line systemic therapy for different degrees of differentiation, there was a higher efficacy of TKI in G1 solitary metastases, with lower efficacy of cytokines compared to multiple metastases. Systemic therapy for G3 tumors demonstrated relatively low TKI efficacy with 27.27% favorable outcomes in solitary metastases. Higher efficacy was noted for single and multiple metastases of RCC. ICI demonstrated efficacy in 70.6% of patients with single and multiple metastases. The efficacy of cytokines in G3 tumor metastases was about the same in single and solitary metastases of RCC (about ½ each) and lower (23.08% favorable outcomes) in multiple metastases

6.1.2 Characterization of the 2nd line of systemic therapy and its effectiveness in patients with metastatic renal cell cancer

Systemic therapy of the 2nd line was performed in 667 (68%) patients with mRCC. The distribution of patients depending on the drug group is presented in Table 6.8.

Table 6.8 – Distribution of mRCC patients according to 2nd line drug group

Drug group	Abs.	%
CHEMOTHERAPY	13	2.0
TKI	604	90.7
Cytokines	12	1.8
ICI	37	5.5
TOTAL	667	100.0

In 2nd line therapy, overall response was achieved in 43 patients (6.4%); complete response was recorded in 4 (0.6%) patients, partial response in 39 (5.8%), stabilization in 330 (49.4%), progression in 243 (36.4%), withdrawal in 22 (3.2%),

and death in 29 (4.3%) mRCC patients (Table 6.5). Of note, disease stabilization (49.4%/42.4%) was recorded more frequently with 2-line systemic therapy than with 1-line therapy (Table 6.9).

Table 6.9 – Treatment response rates in mRCC patients on second-line systemic therapy

Response to therapy	Number of patients	%
Complete response	4	0.6
Partial response	39	5.8
Stabilization	330	49.5
Progression	243	36.4
Withdrawn	22	3.3
Death	29	4.3

Table 6.10 shows that in line 2, ICI showed maximum efficacy with achievement of stabilization in 64.86% of mRCC patients.

Table 6.10 – Frequency of outcomes according to 2nd line treatment in patients with mRCC *(χ^2=41.0890, df=12, p=.000539)*

The drug	Partial response	Stabilization	Progression	Dismissed	Death
CHEMOTHERAPY	0	3 (23.08%)	9 (69.23%)	1 (7.69%)	0
TKI	32 (5.39%)	304 (51.26%)	210 (35.41%)	21 (3.54%)	26 (4.38%)
ICI	7 (18.92%)	24 (64.86%)	4 (10.81%)	0	2 (5.41%)
Cytokines	0	3 (25.00%)	9 (75.00%)	0	0

Progression of the process was most often observed with chemotherapy, while stabilization of the process occurred in half of the cases with TKI. Cytokines caused progression in 75% of cases.

Analyzing the influence of histological characteristics on outcome depending on the group of drugs used, the following results were obtained (Table 6.11).

Table 6.11 – Frequency of outcomes in 2nd line systemic therapy according to drug and histologic variant of RCC (χ^2*=37.0435, df=10, p=.000408)*

Histologic variant/Preparation		Favorable outcome	Unfavorable outcome
Clear-cell	CHEMOTHERAPY	3 (23%)	10 (77%)
	TKI	251 (54.2%)	212 (45.8%)
	ICI	17 (89.5%)	2 (10.5%)
	Cytokines	11 (45.8%)	13 (54.2%)
Non- clear-cell	CHEMOTHERAPY	0	0
	TKI	25 (36.8%)	42 (63.1%)
	ICI	3 (75.0%)	1 (25.0%)
	Cytokines	0	1 (100%)

Table 6.11 shows that immuno-oncologic drugs demonstrated the best efficacy in clear-cell and non-small-cell variants of RCC (89.5% and 75%, respectively). The use of TKI resulted in a favorable outcome in 54.2% of luminal cell variant of RCC and 36.8% of non-small cell variant of RCC.

The use of chemotherapy was more likely to result in an poor outcome for clear cell tumor variants in 77% of mRCC patients. The efficacy of cytokines was found in about half of patients with clear cell tumors.

Table 6.12 shows that ICI demonstrated the best efficacy in the 2nd line of therapy in mRCC patients. Favorable outcome was recorded in 100% of G1 cases and 80% or more in G2 and G3.

Table 6.12 – Frequency of outcomes in 2nd line systemic therapy according to drug and grade of differentiation of mRCC *(χ^2=80.4600, df=17, p=0.000003)*

Grade	The drug	Favorable outcome	Unfavorable outcome
1	CHEMOTHERAPY	0	2 (100.00%)
1	TKI	97 (65.7%)	40 (34.3%)
1	ICI	3 (100.00%)	0
1	Cytokines	3 (42.86%)	4 (57.14%)
2	CHEMOTHERAPY	1 (12.50%)	7 (87.50%)
2	TKI	119 (51.1%)	114 (48.8%)
2	ICI	12 (80.00%)	3 (20.00%)
2	Cytokines	0	3 (100.00%)
3	CHEMOTHERAPY	2 (66.67%)	1 (33.33%)
3	TKI	118 (51.1%)	113 (48.8%)
3	ICI	15 (83.33%)	3 (16.67%)
3	Cytokines	0	2 (100.00%)

The efficacy of TKI in G1 was 65.7%, and half of the patients had a favorable outcome in G2 and G3. The use of chemotherapy demonstrated low efficacy in G1 and G2 tumors. When cytokines were used, favorable outcome was achieved in 42.86% in G1 and was absent in G2 and G3.

6.1.3 Characterization of the 3rd line of systemic therapy and its effectiveness in patients with metastatic renal cell cancer

Third-line systemic therapy was given to 348 (35.5%) patients with mRCC. The distribution of patients depending on the drug group was as follows (Table 6.13).

Table 6.13 – Distribution of patients in mRCC patients according to 3rd line drug group

The drug	Number of patients	%
CHEMOTHERAPY	1	0.3
TKI	322	92.5
Cytokines	5	1.4
ICI	20	5.8
TOTAL	348	100.0

The outcomes of the 3rd line of therapy were distributed as follows (Table 6.14).

Table 6.14 – Distribution of mRCC patients by 3rd line outcome

Response to therapy	Number of patients	%
Complete response	1	0.3
Partial response	17	4.9
Stabilization	188	54.0
Progression	116	33.3
Withdrawn	9	2.6
Death	17	4.9

As shown in Table 6.14, complete response was recorded in 1 (0.3%) patient, partial response in 17 (4.9%), stabilization in 188 (54.0%), progression in 116 (33.3%), withdrawal in 9 (2.6%), and death in 17 (4.9%) patients. Of note, the percentage of mRCC patients with disease stabilization (54.0%) on line 3 therapy increased compared to previous lines of therapy.

When dividing outcomes into conditionally favorable and conditionally unfavorable, no statistical differences were also obtained depending on the treatment given (Table 6.15).

Table 6.15 – Frequency of outcomes according to 3rd line treatment in patients with mRCC *(χ^2=12.6141, df=12, p=.893322)*

The drug	Complete response	Partial response	Stabilization	Progression	Dismissed	Death
CHEMOTHERAPY	0	0	0	1 (100%)	0	0
TKI	1 (0.31%)	15 (4.67%)	170 (53%)	109 (34%)	9 (2.8%)	17 (5.3%)
ICI	0	2 (10%)	14 (70%)	4 (20%)	0	0
Cytokines	0	0	3 (60%)	2 (40%)	0	0

As shown in Table 6.15, ICI was effective in 80% of patients, compared to about 60% when TKI were administered.

Table 6.16 shows that the efficacy of TKI in clear-cell tumor variant was 90%. When TKI was administered, a favorable outcome was observed in 60.5% of patients with clear cell variant of RCC, and in 43.3% of patients with non-clear cell variant.

Table 6.16 – Frequency of outcomes in 3rd line systemic therapy according to drug and histologic variant of RCC *($\chi^{2=}$15.1337, df=10, p=.299079)*

Histologic variant/Preparation		Favorable outcome	Unfavorable outcome
Clear-cell	CHEMOTHERAPY	0	1 (100%)
	TKI	172 (60.5%)	112 (39.5%)
	ICI	9 (90%)	1 (10%)
	Cytokines	3 (60%)	2 (40%)
Non- clear-cell	CHEMOTHERAPY	0	0
	TKI	13 (43.3%)	17 (46.7%)
	ICI	0	1 (100%)
	Cytokines	0	0

In contrast to the histologic variant, the degree of RCC differentiation had an impact on outcome in line 3 in a drug-dependent manner (Table 6.17).

Table 6.17 – Frequency of outcomes in 3rd line systemic therapy depending on drug and grade of differentiation in mRCC patients *(χ^2=65.2216, df=17, p=.000313)*

Grade	The drug	Favorable outcome	Unfavorable outcome
1	CHEMOTHERAPY	0	0
1	TKI	53 (69.64%)	26 (30.36%)
1	ICI	3 (100.00%)	0
1	Cytokines	2 (50%)	2 (50%)
2	CHEMOTHERAPY	0	1 (100%)
2	TKI	66 (59.55%)	48 (40.45%)
2	ICI	10 (76.92%)	3 (23.08%)
2	Cytokines	1 (100%)	0
3	CHEMOTHERAPY	0	0
3	TKI	67 (56%)	61 (44%)
3	ICI	2 (66.7%)	1 (33.3%)
3	Cytokines	1 (100%)	0

Table 6.17 shows that TKI gave a favorable outcome in G1 tumors in 100% of cases, and as differentiation decreased (59-56%) its efficacy decreased, but it was still the best in comparison with other groups of drugs. Favorable outcome with TKI was observed regardless of the differentiation degree in more than half of cases, its frequency decreased from 69.64% in G1 to 56% in G3.

6.1.4 Characterization and efficiency of lines 4-6 systemic therapy in patients with metastatic renal cell cancer

Fourth-line systemic therapy was given to 138 (14.1%) mRCC patients, fifth-line therapy was given to 49 (5%) patients, and sixth-line systemic therapy was given to 23 (2.3%) patients.

The distribution of cases according to drug group is presented in Table 6.18.

Table 6.18 – Distribution of cases according to 4th-6th line drug group in mRCC patients

The drug	Number of patients	%
CHEMOTHERAPY	4	1.9
TKI	184	88.9
Cytokines	4	1.9
ICI	15	7.3
TOTAL	207	100.0

The cumulative incidence of the various responses in lines 4-6 of therapy in mRCC patients is summarized in Table 6.19.

Table 6.19 – Frequency of observed responses to systemic therapy in lines 4-6 of mRCC patients

Response to therapy	Number of patients	%
Partial response	13	6.3
Stabilization	85	41.0
Progression	91	44.0
Withdrawn	7	3.4
Death	11	5.3

According to Table 6.19, progression of the process was most often observed in mRCC patients on lines 4-6 of systemic therapy, and stabilization was observed somewhat less frequently. Partial response was the most favorable outcome and was observed in only 6.3% of cases, almost as often patient death was registered (5.3%).

The following statistical differences were found in the incidence of outcomes according to treatment (Table 6.20).

Table 6.20 shows that TKI therapy achieved a favorable outcome in 73.33% of mRCC patients. Partial response was extremely rare with TKI (4.35%), and disease progression was observed almost as often as stabilization.

Table 6.20 – Frequency of outcomes according to treatment at lines 4-6 in patients with mRCC *(χ^2=37.3405, df=12, p=0.000197)*

The drug	Partial response	Stabilization	Progression	Dismissed	Death
CHEMOTHERAPY	0	0	3 (75.0%)	0	1 (25.0%)
TKI	8 (4.35%)	79 (42.93%)	82 (44.57%)	6 (3.26%)	9 (4.89%)
ICI	5 (33.33%)	6 (40.0%)	4 (26.67%)	0	0
Cytokines	0	0	2 (50.0%)	1 (25.0%)	1 (25.0%)

Administration of chemotherapy and cytokines always ended with an unfavorable outcome.

Comparison of the incidence of outcomes in line 4 therapy according to the histologic type of mRCC showed no statistically significant differences (Table 6.21).

Table 6.21 – Frequency of outcomes in 4th-6th lines of systemic therapy depending on drug and histologic variant in mRCC patients *(χ^2=19.6932, df=10, p=0.032)*

Histologic variant/Preparation		Favorable outcome	Unfavorable outcome
Clear-cell	CHEMOTHERAPY	0	3 (100%)
	TKI	79 (49.07%)	82 (50.93%)
	ICI	8 (88.89%)	1 (11.11%)
	Cytokines	0	4 (100%)
Non- clear-cell	CHEMOTHERAPY	0	1 (100%)
	TKI	5 (33.33%)	10 (66.67%)
	ICI	0	1 (100%)
	Cytokines	0	0

Table 6.21 shows that there were no differences in the frequency of outcomes depending on the histologic variant of mRCC with different types of treatment at follow-up. TKI with checkpoint inhibitors was effective in all patients with the clear cell variant of the tumor. When TKI was administered, a favorable outcome was observed in clear-cell and non-small-cell variants of mRCC in 49.07% and 33.33% of patients.

The degree of tumor differentiation conversely influenced the outcome rate in a drug-dependent manner (Table 6.22).

Table 6.22 – Frequency of outcomes in lines 4-6 of systemic therapy depending on drug and grade of differentiation in mRCC patients *(χ^2=40.8920, df=17, p=0.000967)*

Grade	The drug	Favorable outcome	Unfavorable outcome
1	CHEMOTHERAPY	0	0
1	TKI	31 (67.39%)	15 (32.61%)
1	ICI	3 (100%)	0
1	Cytokines	0	2 (100%)
2	CHEMOTHERAPY	0	0
2	TKI	28 (38.89%)	44 (61.11%)
2	ICI	5 (71.43%)	2 (28.57%)
2	Cytokines	0	2 (100%)
3	CHEMOTHERAPY	0	4 (100%)
3	TKI	29 (43.94%)	37 (56.06%)
3	ICI	3 (60.0%)	2 (40.0%)
3	Cytokines	0	0

Table 6.22 shows that the efficacy of all groups of drugs continued to decrease in the 4th-6th lines of therapy for mRCC patients. However, TKI demonstrated the highest efficacy, which gradually decreased as the degree of tumor differentiation decreased. TKI demonstrated a sharply decreasing to 38.89% rate of favorable outcome for G2 tumors, which was slightly higher for G3 tumors.

Thus, we analyzed the outcome of therapy by lines. The best results with systemic therapy in all lines of mRCC patients were obtained with immuno-oncologic drugs and TKI. Regardless of the number of affected organs, number of metastases and tumor differentiation degree, the frequency of favorable outcome was higher with immunotherapy than with other treatment options.

6.2 Impact on survival rates of different variants combination treatment for metastatic renal cell cancer

6.2.1 Analyzing the impact on patient survival rates with metastatic renal cell cancer depending on the from combinations of different systemic therapy drugs

Further analysis by line and drug in each line was performed excluding cytokine therapy and chemotherapy that was performed in the pre-targeting era.

Systemic drug therapy in lines 1-3 was performed with the following groups of drugs: TKI, ICI (PD-1, PD-L1), and m-TOR inhibitors.

6.2.1.1 Comparative analysis of patients with metastatic renal cell cancer and the impact on survival rates depending on the type of systemic treatment of single-line therapy

One line of systemic therapy was performed in 376 mRCC patients, of which 356 (94.7%) patients received TKI, 11 (2.9%) patients received ICI, and 9 (2.4%) patients received m-TOR inhibitor therapy. The duration of systemic therapy for these groups ranged from 1 to 104 months (15.1 months on average) for TKI; from 3 to 12 months (7 months on average) for ICI; from 1 to 39 months (12 months on

average) for m-TOR inhibitors. Patient characteristics according to systemic drug group are presented in Table 6.23.

Table 6.23 – Comparative analysis of clinical and morphologic parameters of patients who received 1 line of systemic therapy depending on the drug

Signs	Number of patients	TKI	ICI	m-TOR inhibitors	Significance level
Clear-cell	abs.	311	11	5	χ^2=9.5; p=0.008
	%	95.1	3.4	1.5	
Non- clear-cell	abs.	45	0	4	
	%	91.8	0	8.2	
Grade 1	abs.	170	1	5	χ^2=6.7; p=0.035
	%	96.6	0.6	2.8	
Grade 2, 3	abs.	186	10	4	
	%	93.0	5.0	2.0	
Metastasis to 1 organ	abs.	134	5	4	χ^2=3.0; p=0.553
	%	93.7	3.5	2.8	
Metastasis to 2 organs	abs.	113	1	3	
	%	96.6	0.8	2.6	
Metastasis to 3 or more organs	abs.	109	5	2	
	%	94.0	4.3	1.7	
ECOG 1	abs.	115	5	1	χ^2=2.7; p=0.26
	%	95.1	4.1	0.8	
ECOG 2	abs.	241	6	8	
	%	94.5	2.4	3.1	
Favorable prognosis	abs.	67	1	1	χ^2=1.1; p=0.89
	%	97.0	1.5	1.5	
Intermediate prognosis	abs.	99	3	3	
	%	94.2	2.9	2.9	
Poor prognosis	abs.	190	7	5	
	%	94.0	3.5	2.5	

Continuation of Table 6.23

Signs	Number of patients	TKI	ICI	m-TOR inhibitors	Significance level
Synchronous metastases	abs.	164	8	5	χ^2=3.3; p=0.19
	%	92.7	4.5	2.8	
Metachronous metastases	abs.	192	3	4	
	%	96.5	1.5	2	

Table 6.23 shows that m-TOR inhibitors were more frequently prescribed to patients with non-small cell variants of mRCC. TKI and m-TOR inhibitors were significantly less frequently prescribed for tumors with a high degree of differentiation. There were no significant differences in the other comparable characteristics. The OS rates are presented in Figure 6.1.

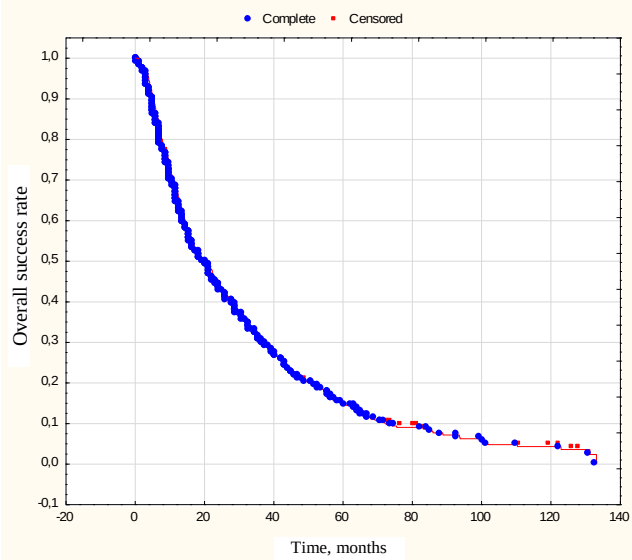
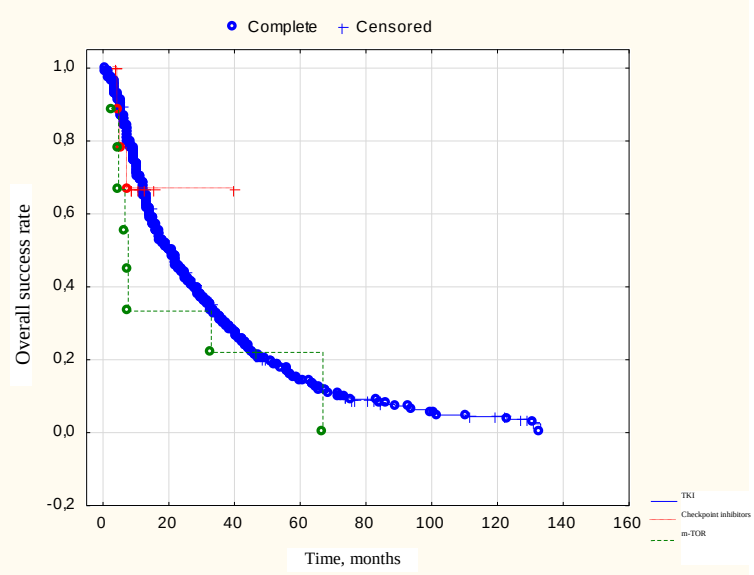


Figure 6.1 OS rates of patients with mRCC (N=376),
who have received one line of systemic therapy

The 3-year, 5-year, and 10-year OS of mRCC patients who received a single line of systemic therapy were 30.3±1.5%, 14.7±1.4%, and 4.2±1.3%, respectively. The median OS was 19 months (Figure 6.2).



p=0,27

Figure 6.2 – OS rates of mRCC patients (N=376) who received one line of systemic therapy depending on the drug of systemic therapy

Figure 6.2 shows that the 3-year and 5-year OS of patients who received one line of TKI therapy were 25.7±1.5% and 17.8±1.3%; for the TKI group, the 1- and 3-year OS were 61.2±1.6%; for the m-TOR inhibitor group, the 3- and 5-year OS were 21.2±1.5%, respectively. The median OS for TKI and m-TOR was 18 and 6 months, respectively. The median OS for TKI was not reached. Thus, in the current study, there was no difference in the OS in mRCC patients who received only one line of therapy (p=0.27).

Thus, there were no statistical differences in survival rates in mRCC patients who received 1 line of systemic therapy, depending on the drug.

6.2.1.2 Comparative analysis of patients' indicators with metastatic renal cell cancer and the impact on survival rates depending on the type of systemic therapy when given in two lines of therapy

Systemic therapy in 2 lines was given to 272 mRCC patients, who were categorized into 4 groups depending on different combinations of systemic drugs:

- TKI + TKI – 211 (77.3%) patients;
- TKI + ICI and – ICI + TKI – 17 (6.2%) patients, of which 15 (5.5%) patients received TKI in the first line, ICI in the first line was performed in 2 (0.7%) patients;
- TKI + m-TOR inhibitor – 32 (11.7%) patients;
- m-TOR inhibitor + TKI – 12 (4.4%) patients.

The duration of systemic therapy for these groups was:

- TKI + TKI – 1 to 135 months (32.9 months on average);
- TKI + ICI – 4 to 48 months (19.3 months on average);
- ICI + TKI – 10 to 23 months (16, 5 months on average);
- TKI + m-TOR inhibitor – 15 to 73 months (32.7 months on average);
- m-TOR inhibitor + TKI – from 2 to 37 months (13.7 months on average).

The OS indicators are presented in Figure 6.3.

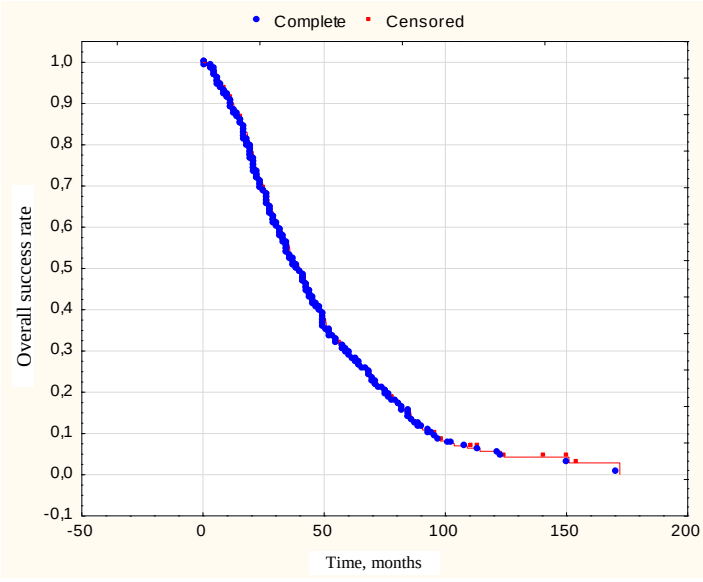
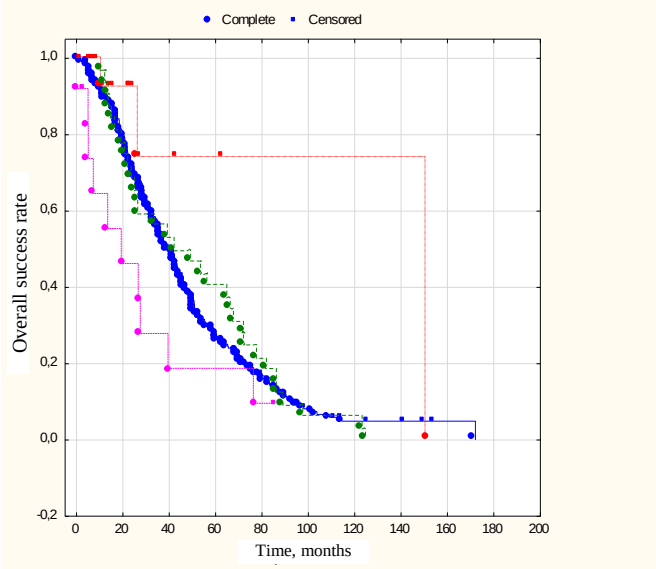


Figure 6.3 – OS of patients (N=272) with mRCC, who have received two lines of systemic therapy

The presented Kaplan-Meier curves demonstrated that the 3-year, 5-year, and 10-year OS of all mRCC patients who received two lines of systemic therapy were 43.7±1.7%, 29.8±1.6%, and 7.6±1.3%, respectively. The median OS was 37 months.

The presented Kaplan-Meier curve (Figure 6.4) shows that the 3-year, 5-year and 10-year OS of patients who received two lines of therapy were – for the first subgroup – 50.2±1.6%, 29.5±1.4% and 5.4±1.3%, respectively; for the second subgroup – 76,9±1,8%; for the third subgroup – 56,2±1,6%, 40,6±1,5% and 6,2±1,3%; for the fourth subgroup – 28,2±1,4%, 18,8±1,4% and 0% respectively. Meanwhile, the median OS of 45, 40, and 20 were months for subgroups 1, 3, and 4, respectively. The median OS for subgroup 2 was not reached. Thus, in the current study, there were no differences in the OS in mRCC patients who received two lines of therapy (p=0.007).



p=0,007

Figure 6.4 – Comparison of OS rates of patients with mRCC (N=272) who received two lines of systemic therapy, depending on the combination of drugs

Thus, the combination of drugs had no effect on OS. The best results were demonstrated by the combination of TKI+ICI, the worst – by m-TOR inhibitor+TKI.

6.2.1.3 Comparative analysis of patients' indicators with metastatic renal cell cancer and the impact on survival rates depending on the type of systemic therapy when given in three lines of therapy

Only 3 lines of systemic therapy were given to 149 patients who were categorized into 3 groups according to different drug combinations:

– TKI + TKI + TKI – 78 (45.1%) patients;
– TKI + TKI + m-TOR inhibitor – 46 (26.6%) patients;
– TKI + m-TOR inhibitor + TKI – 25 (14.5%) patients.

Duration of systemic therapy:

– TKI + TKI + TKI + TKI – 5 to 113 months (38.2 months on average);
– TKI + TKI + M-TOR – 6 to 105 months (36, 6 months on average);
– TKI + M-TOR + TKI – 15 to 69 months (37.7 months on average).

Figure 6.5 shows that the 3-year, 5-year and 10-year OS of all patients who received the three lines of systemic therapy were 59.2±1.6%, 38.8±1.5% and 8.9±1.3%, respectively. At the same time, the median OS was 49 months.

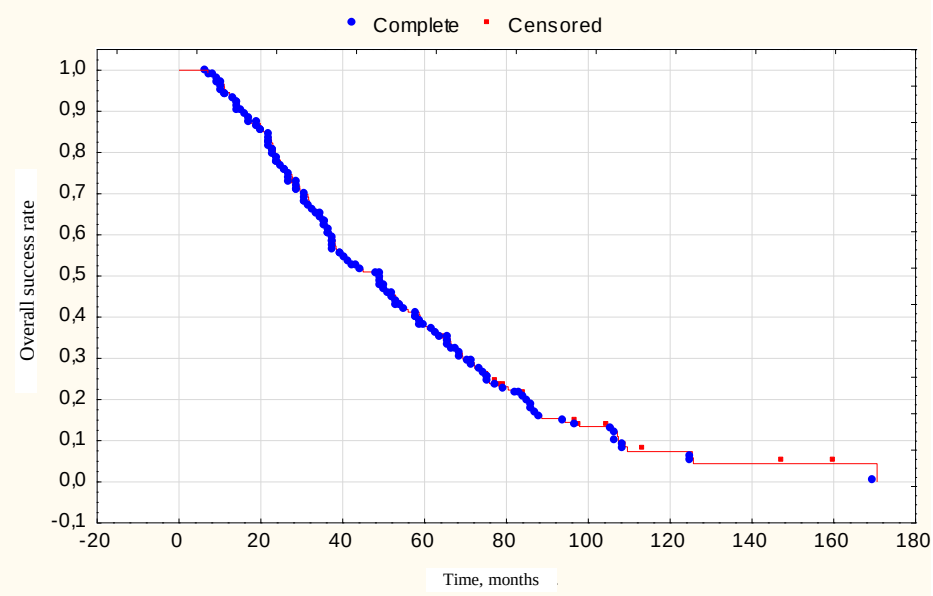
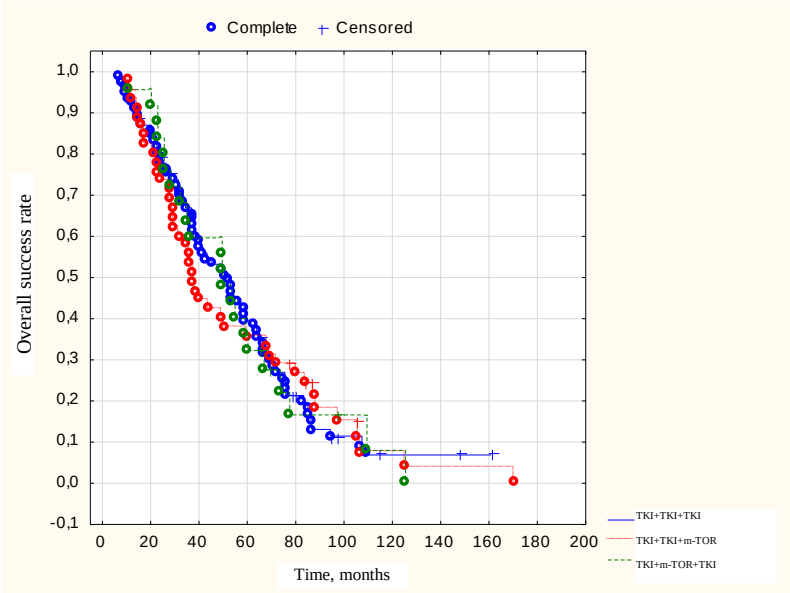


Figure 6.5 – OS rates of patients with mRCC (N=149), who have received three lines of systemic therapy

The presented Kaplan-Meier curve (Figure 6.6) shows that the 3-year, 5-year, and 10-year OS of patients who received three lines of therapy were 54.7±1.7%, 39.7±1.5%, and 8.6±1.3% for the first subgroup; 44.6±1.6%, 35.6±1.5%, and 4.6±1.3% for the second subgroup; 60.0±1.7%, 32.1±1.5%, and 9.2±1.3% for the third subgroup, respectively. The median OS was 55, 39, and 53 months, respectively. Thus, in the current study, there was no difference in the OS in mRCC patients who received three lines of therapy (p=0.85).



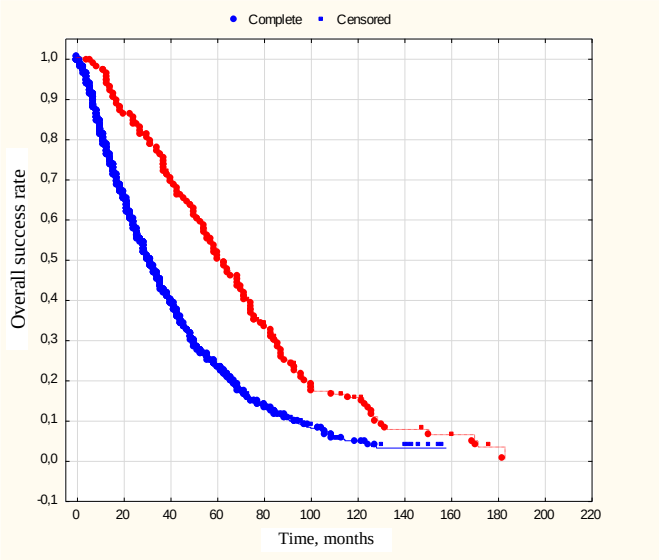
p=0.85

Figure 6.6 – Comparison of OS rates of patients with mRCC (N=149) who received three lines of systemic therapy, depending on the combination of targeted therapies

Thus, the combination of drugs in three lines of systemic therapy had no effect on survival rates in mRCC patients.

6.3 Effect of systemic therapy regimen on survival rates in patients with metastatic renal cell cancer

Additionally, the effect of systemic therapy regimen on survival rates of mRCC patients was analyzed (Figure 6.7).



p<0.001

Figure 6.7 – OS indicators of patients with mRCC
depending on the regimen of the prescribed systemic therapy

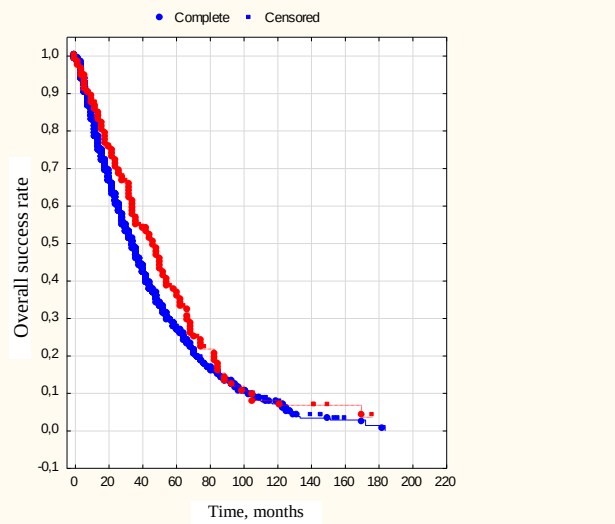
The presented Kaplan-Meier curves show that the 3-year and 5-year OS rates in the group of patients with intermittent and continuous systemic therapy were 78.2±1.5% and 50.1±1.6%, 42.2±1.5% and 23.3±1.3%, respectively. The median OS also differed and was 60 and 30 months, respectively.

Thus, in the conducted study, there were significant differences in the rates of OS in mRCC patients depending on the regimen of systemic therapy (p<0.001).

6.4 Impact on survival rates of patients with metastatic renal cell cancer with radiation therapy

Radiation therapy was given to 131 mRCC patients (Figure 6.8).

The presented Kaplan-Meier curves show that the 3-year and 5-year OS rates in the groups of mRCC patients with and without radiation therapy for metastases were 61.7±1.7% and 36.2±1.5%, 49.7±1.6% and 26.9±1.5%, respectively. The median OS also differed and was 44 and 36 months, respectively.



p=0.004

Figure 6.8 – Comparison of overall survival rates of patients with mRCC depending on the presence/absence of radiation therapy.

Thus, in the conducted study, there were significant differences in OS rates in mRCC patients depending on radiation therapy (p=0.004).

Conclusion

According to the results of the study, the best treatment results in all lines of therapy in mRCC patients were obtained with ICI and TKI. ICI demonstrated the highest frequency of favorable outcomes even in tumors with less favorable prognosis (non-small cell variant, low degree of differentiation), which was not observed for other groups of drugs. The tendency to decrease the frequency of favorable outcomes when switching to a new line of therapy was noteworthy. When patients were assigned to a new line of therapy, a decrease in the rate of complete and partial response was observed, but the rate of progression also decreased. Therefore, it is necessary to carefully approach the choice of the first-line drug to stop or slow down tumor progression. mRCC patients with multiple metastases and involvement of more organs more often had an unfavorable outcome, which makes us think about the existence of "tumor burden", and may require revision of drug dosages taking into account their toxicity depending on the number of metastases.

Chapter 7
CREATING MATHEMATICAL MODELS FOR PREDICTING SURVIVAL AND OUTCOMES OF PATIENTS WITH METASTATIC RENAL CELL CANCER

7.1 Logistic regression model for forecasting the indicators of the 5-year overall survival and its estimation using ROC analysis

The method of logistic regression was chosen as a mathematical and statistical method of solving the problem, the main condition for the use of which is the dichotomous nature of the predicted trait, as well as qualitative predominantly dichotomous trait predictors.

The results of the primary calculations presented in Table 7.1 show that not all attributes included in the model have a statistically significant impact on the EI indicators. The reason may be either really insufficient influence of some factors or strong correlation of some attributes among themselves (r>0.7). In this case, one factor takes on the load of the second, and the latter loses its significance (p>0.05).

Table 7.1 – Results of calculation of the ESRfficients of the multifactor model for predicting the 5-year PFS of mRCC patients

№	Name of attributes and their gradations	Beta	Standard Error	t-value	exponent beta	Wald Statist.	p
1	Age less than 60 years	0.09	0.07	1.16	1.09	1.36	0.2442
2	RCC Option 2	0.23	0.11	2.12	1.26	4.50	0.0338
3	Degree of tumor differentiation 2	0.83	0.06	13.39	2.29	179.40	0.0000
4	Synchronous/Metachronous	-0.44	0.16	-2.69	0.65	7.24	0.0071
5	Number of mts	0.61	0.09	6.92	1.84	47.91	0.0000
6	Localization of mts	-0.33	0.07	-5.04	0.72	25.42	0.0000

Continuation of Table 7.1

№	Name of attributes and their gradations	Beta	Standard Error	t-value	exponent beta	Wald Statist.	p
7	Hemoglobin level	0.31	0.05	6.81	1.36	46.43	0.0000
8	Alkaline phosphatase level	-0.01	0.09	-0.15	0.99	0.02	0.8791
9	LDH level	0.00	0.09	-0.04	1.00	0.00	0.9708
10	Total calcium level	-0.60	0.29	-2.11	0.55	4.45	0.0349
11	Ionized calcium level	-0.06	0.07	-0.94	0.94	0.88	0.3484
12	Neutrophil count	-0.01	0.06	-0.16	0.99	0.03	0.8728
13	ESR level	-0.09	0.09	-1.04	0.91	1.09	0.2965
14	Platelet count	0.07	0.06	1.30	1.07	1.69	0.1939
15	ECOG Status	0.45	0.08	5.51	1.58	30.40	0.0000

As Table 7.1 shows, not all factors included in the model showed a statistically significant effect on survival time. Therefore, the next step in calculating the optimal model based only on statistically significant factors was a step-by-step selection of the most significant ones into the model.

The result of the model solution is the probability, in the range from 0 to 1, of the outcome of interest, in our case survival for 5 years. The outcome of model selection is presented in Table 7.2 and Formula 1. The resulting logistic regression model using the 4 most significant prognostic factors was statistically significant ($p<0.001$) and 93.3% classifiable (Table 7.2). The sensitivity of the model was 98.3% and specificity was 62.3%.

The classification of the results of the 5-year follow-up by survivor-death using the logistic regression model compared to those observed in the experiment is presented in Table 7.3.

Table 7.2 – Features included in the model, their coefficients, significance level and odds ratio

Signs and their gradations	Symbols	Coefficients	Significance level, p	Odds ratio		
				significance	-95% DI	+95% DI
Characteristics of metastases: solitary – 1, single – 2, multiple – 3	X1	-0.468	0.078	0.626	0.372	1,054
Hemoglobin: more than 106 – 0, less than 106 – 2	X2	-0.669	0.016	0.512	0.298	0,882
ECOG status: (0, 1) – 1, (2, 3, 4) – 2	X3	-0.466	0.209	0.628	0.303	1,300
Degree of tumor differentiation: G1 – 1, G2 – 2, G3 – 3	X4	-2.965	<0.001	0.052	0.025	0,105
Constant		-6,41	<0.001	609.1	89.4	4150.1

Table 7.3 – Classification of 5-year follow-up results by survivor-death using logistic regression model compared to those observed in the experiment

Result observations	Forecast result			Total
	% match	survived	dead	
Survived	62.3	48	29	77
Dead	98.3	8	467	475
Total in the forecast	93.3	56	496	552

The model for calculating the probability of the outcome of 5-year survival is as follows:

$$\hat{y} = \frac{\exp(-6{,}41 + 0{,}47 \times X1 + 0{,}67 \times X2 + 0{,}46 \times X3 + 2{,}96 \times X4)}{1 + \exp(-6{,}41 + 0{,}47 \times X1 + 0{,}67 \times X2 + 0{,}46 \times X3 + 2{,}96 \times X4)}, \quad (1)$$

The value of the traits in a particular patient is entered into the formula and the equation is solved. The result is a value $\hat{y}$which shows the probability of the patient's survival. The threshold for assigning a patient to the group of dead or survivors is 0.5. If the result is less than 0.5, the patient will most likely not live more than 5 years, if it is equal to or greater than 0.5, the patient is more likely to live 5 years or more.

The sensitivity and specificity of the model were confirmed by ROC-analysis, which confirmed high sensitivity and sufficient specificity of the logistic regression model. The area under the curve was 93.9% (95 CI – 91.4÷96.5%), which indicates the excellent quality of the model. The ROC-curve is presented in Figure 7.1.

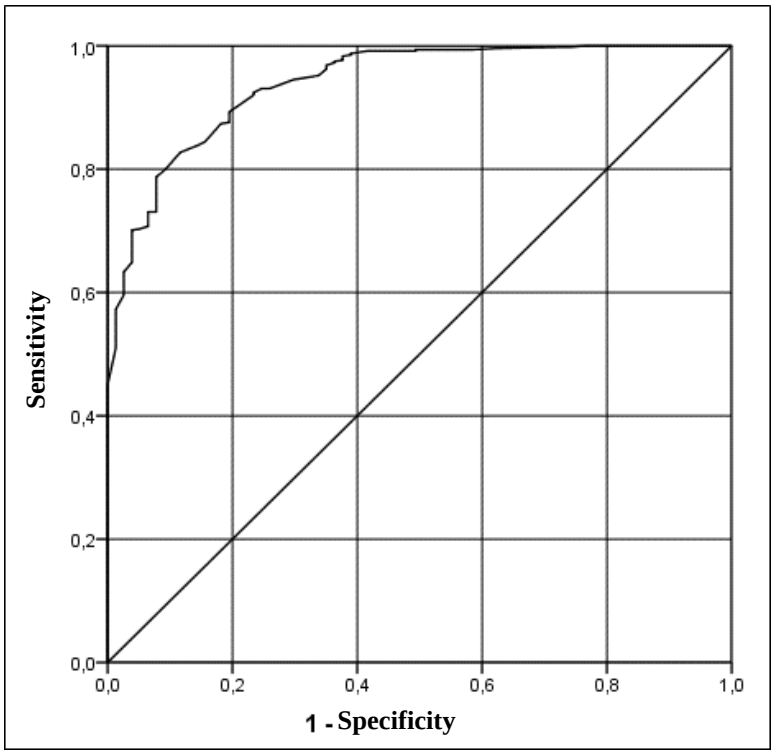


Figure 7.1 – ROC curve of the diagnostic ability of the logistic regression model for predicting 5-year survival rate

When determining the cut-off point, we were guided by the rule of the maximum sum of sensitivity and specificity, which amounted to 1.968 (sensitivity 89.3% + specificity 80.5%), which allows us to take 0.8 instead of the threshold of 0.5 when interpreting the results of the decision. Less than 0.8 – 5-year survival is unlikely, more than 0.8 the probability of survival increases. In this case, the

sensitivity of the model may decrease to 89.3%, and the specificity may increase to 80.5% with a cut-off point equal to 0.806 (80.6%).

It is important to note that the logistic regression model estimates the probability of survival between 0 and 1. The higher the result obtained, the greater the probability of living more than 5 years.

The role of each of the attributes included in the model is assessed by examining the model itself. Thus, changing a predictor by one grade increases or decreases the probability of survival by a certain fraction 1.

For example, the patient's examination reveals multiple metastases (3), hemoglobin level less than 106 (2), ECOG status – 2, and Fuhrman tumor differentiation grade – G3 (3). When solving the equation with these values, the probability of 5-year survival is only 0.002 or 0.2%. If the patient has: single metastasis (2), hemoglobin level less than 106 (2), ECOG status 2 and tumor differentiation degree according to Fuhrman – G2 (2), the probability of 5-year survival will be 0.061 or 6.1%. In the situation when the patient has the following signs: single metastases (2), hemoglobin level less than 106 (2), ECOG status equal to 1 and tumor differentiation degree according to Fuhrman – G1 (1), then the probability of 5-year survival will be 0.670 or 67.0%. Changing the number of metastases from sporadic to solitary, with the same values of other factors, will increase the probability to 0.764 or 76.4%.

Thus, the logistic regression model for predicting 5-year OS was statistically significant ($p<0.001$) and sufficiently classifiable (93.3%). In addition, it allows us to evaluate the role of each factor in producing a predictive value for the probability of 5-year survival. ROC analysis confirmed the excellent quality of the model – the area under the curve was 93.9% (95DI – 91.4÷96.5%), sensitivity 89.3% and specificity 80.5% with a cut-off point equal to 80.6%.

A design patent was obtained based on this model (Figure 7.2).

ПАТЕНТ

НА ПРОМЫШЛЕННЫЙ ОБРАЗЕЦ

№ 134774

СХЕМА-АЛГОРИТМ МОДЕЛИ ДЛЯ ПРОГНОЗИРОВАНИЯ ВЫЖИВАЕМОСТИ БОЛЬНЫХ мПКР

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Заявка № 2022504102
Приоритет(ы) промышленного образца 21 сентября 2022 г.
Дата государственной регистрации в Государственном реестре промышленных образцов Российской Федерации 09 января 2023 г.
Срок действия исключительного права на промышленный образец истекает 21 сентября 2027 г.

Руководитель Федеральной службы по интеллектуальной собственности

Ю.С. Зубов

Figure 7.2 – Design patent
"A schema-algorithm model for predicting survival rates of mRCC patients"

Based on the results of single-factor analysis, which provided the study of the degree of influence of various predictor factors (attributes) on patients' survival time, we proceeded to the next stage of the study – calculation of a multifactor model for predicting survival time based on the most significant predictors. The results of the initial calculations showed that not all the attributes included in the initial data matrix have a statistically significant effect on the OR. The reason may be either really insufficient influence of some factors or strong correlation of some attributes among themselves ($r>0.7$). In this case, one factor takes on the load of the second, and the latter loses its significance ($p>0.05$).

Therefore, the next step in the calculation of the optimal model based on only statistically significant factors was a step-by-step selection of the most significant of them into the model – the result is shown in Table 7.4.

Table 7.4 – Results of calculation of coefficients of the multifactor model for predicting survival time based on statistically significant factors

No. of nos.	Name traits and their gradations	Model coefficients	Significance level, p	Relative risk		
				significance	lower gr. 95% CI	upper gr. 95% CI
1	Variant of RCC: light-cell – 1, other – 2	0.28	0.0105	1.32	1.07	1.64
2	Differentiation: high – 1, moderate and low – 2	0.60	0.0000	1.82	1.53	2.16
3	Type of metastases: synchronous – 1, metachronous – 2	-0.59	0.0000	0.55	0.46	0.66
4	Number of metastases: solitary – 1, single – 2, multiple –3	0.48	0.0000	1.62	1.40	1.87
5	Number of organs with metastasis: 1, 2, (3 or more) – 3	-0.25	0.0000	0.78	0.70	0.87
6	IMDC: favorable – 1, intermediate – 2, poor – 3	0.81	0.0000	2.25	2.00	2.53
7	TKI: applied – 1, not applied – 0	-0.14	0.0594	0.87	0.75	1.01

The signs of the model coefficients show that the majority of factors increase the intensity of lethal outcomes with increasing levels. At the same time, the greatest risk in the intensity of lethal outcomes is contributed by such features as: IMDC with a risk of 2.25, tumor differentiation with a risk of 1.82, and type of metastases with a risk of 1.62.

The mathematical interpretation of the model is rather complicated, so we will give its graphical representation. Below we present the graphs of overall survival at the average values of the factors included in the model, at their worst combination,

the most favorable combination and for the factors identified in a particular patient (Table 7.5, Figures 7.3-7.6).

Table 7.5 – Input data for calculations of variants of the overall survival rate models

№ np	Name of attributes and their gradations	Variants of factor values			
		average values	favorable	unfavorable	patient K1
1	Variant of RCC: clear-cell – 1, another – 2	1.116	1	2	1
2	Differentiation: high – 1, moderate to low – 2	1.443	1	2	2
3	Type of metastasis: synchronous – 1, metachronous – 2	1.589	1	2	1
4	Number of metastases: solitary – 1, single – 2, multiple –3	2.559	0	2	2
5	Number of organs with metastasis: 1, 2, (3 or more) – 3	1.884	1	2	2
6	IMDC: favorable – 1, intermediate – 2, poor – 3	2.169	1	3	2
7	TKI: applied – 1, not applied – 0	0.547	1	2	1

It follows from Figure 7.3 that the OS rates of mRCC patients are on average about 5% of operated patients. The median OS is in the range from 4.5 to 5 years. The lower quartile is close to 3 years, and the upper quartile is about 6.5 years.

With a favorable combination of prognostic factors (Figure 7.4), OS rates reach more than 60%, the median OS is out of reach, and the upper quartile is around 9 years.

In unfavorable combination of prognostic factors (Figure 7.5), the OS did not exceed 4 years. The upper quartile is slightly more than 6 months, the median OS is slightly more than a year, and the lower quartile is between 1.5 and 2 years.

Figure 7.6 shows the curve of OS indicators of patient K., who had the following values of predictor factors:

1. Variant of RCC: clear-cell – 1.
2. Differentiation: moderate to low – 2.
3. Type of metastases: synchronous – 1.
4. Number of metastases: single – 2.
5. Number of organs with metastases: 2.
6. IMDC forecast: intermediate – 2.
7. TKI: not applied – 0.

From the analysis of Figure 7.6, it can be seen that the OS indicators could be around 7.5 years. The median term is close to 3 years, the upper quartile will be 1 to 1.5 years, and the lower quartile will be 3.5 to 4 years.

Thus, based on the 7 most statistically significant factors, a statistically significant ($p<0.001$) model for assessing the OS indicators of patients with mRCC was obtained.

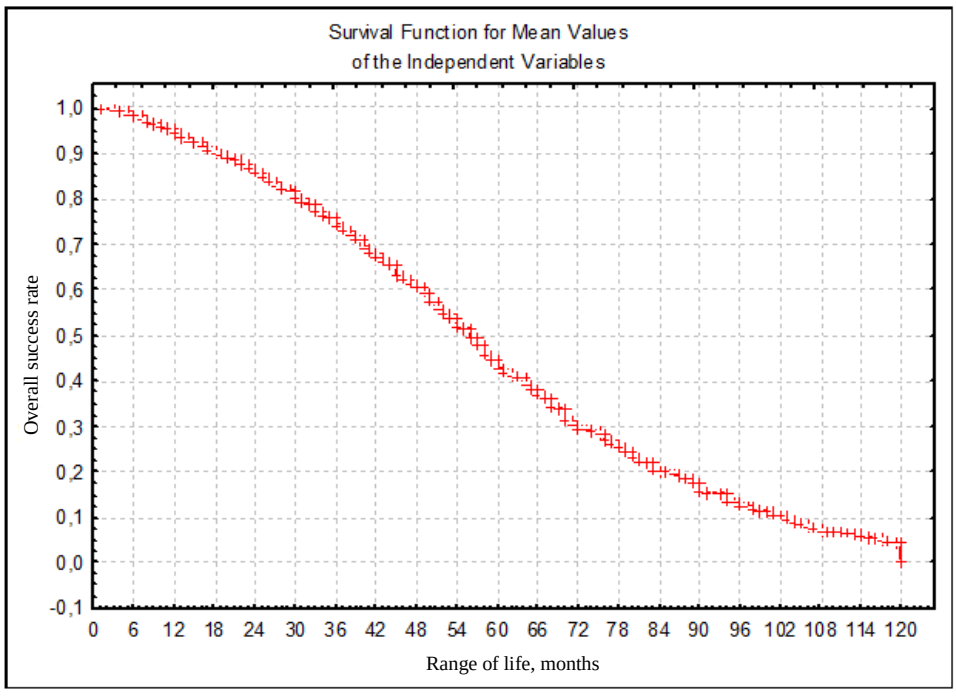

Figure 7.3 – Model of OS indicators
at average values of predictor factors in a mRCC patient

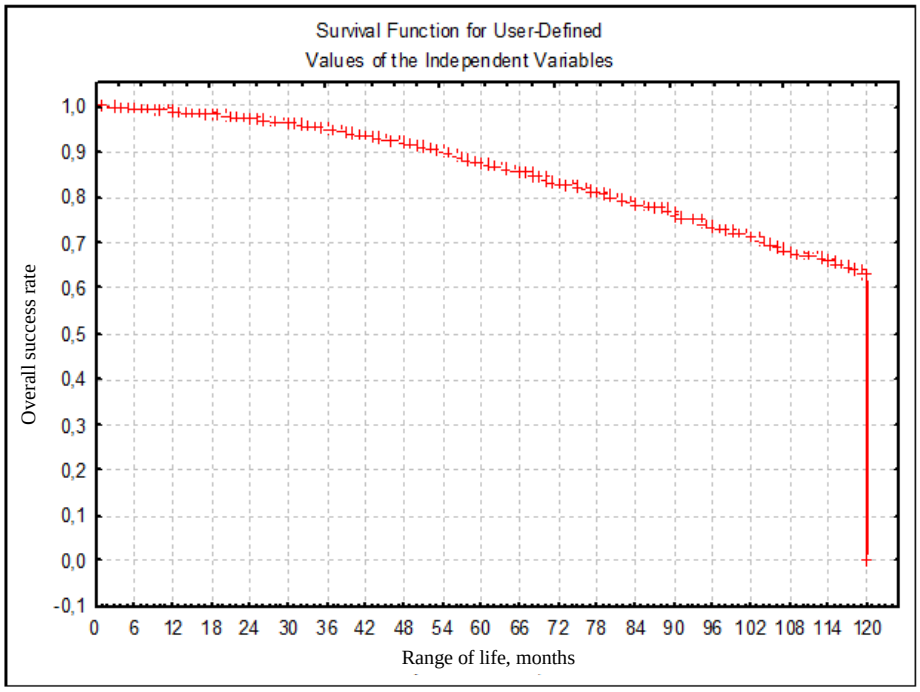

Figure 7.4 – Model of OS indicators

at favorable values of predictor factors in a patient with mRCC

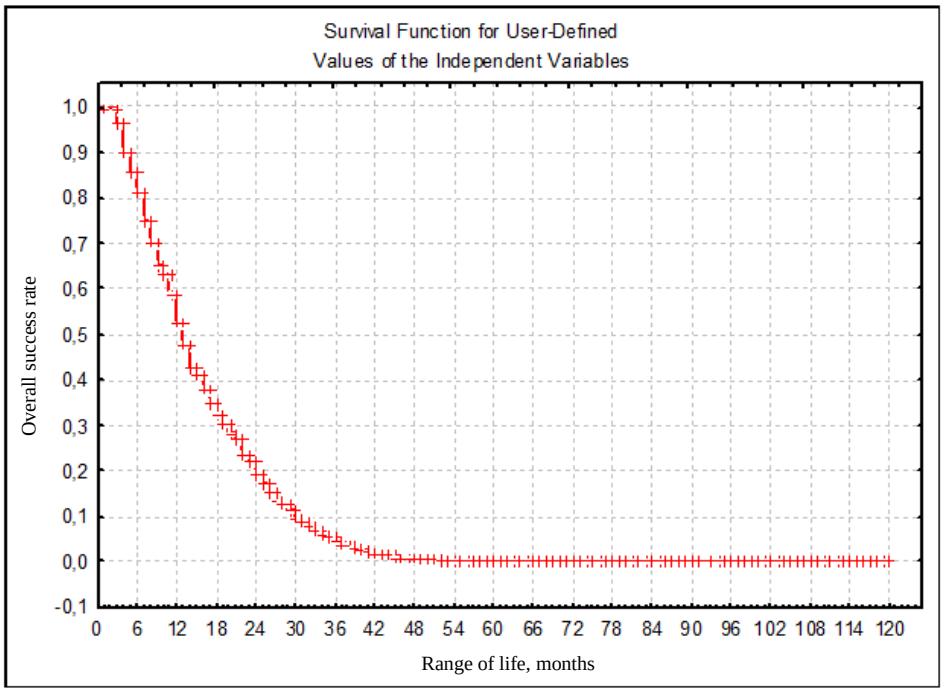

Figure 7.5 – Model of OS indicators

at unfavorable values of predictor factors in a patient with mRCC

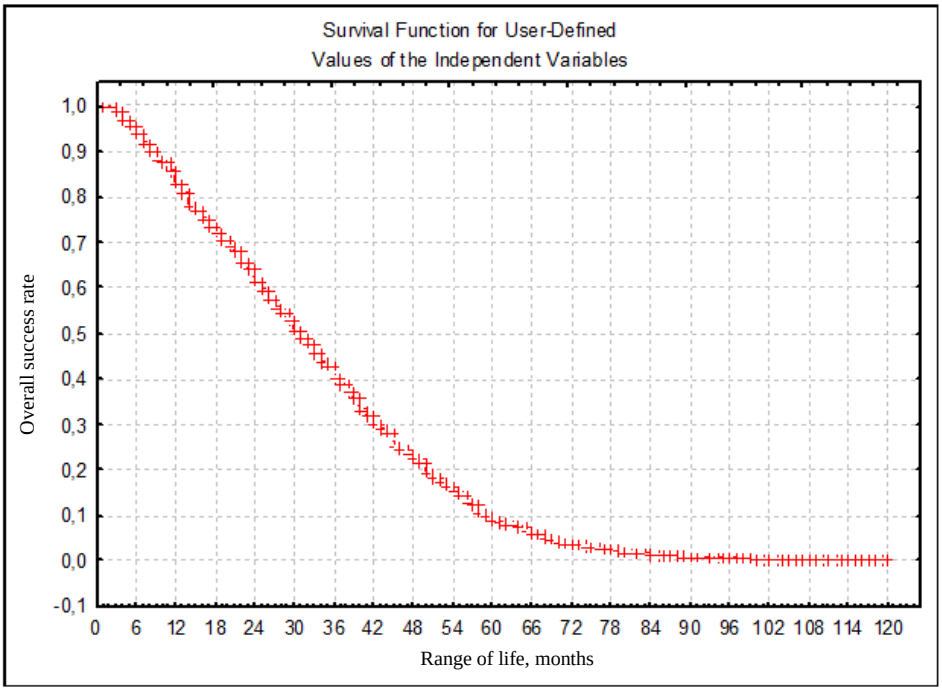

Figure 7.6 – Model of OS indicators
at specific values of predictor factors in a C mRCC patient

7.2 Creating a modified predictive model in patients with metastatic renal cell cancer based on the factors identified in the study

7.2.1 Creating a prognostic model in 981 patients with metastatic renal cell cancer based on the results of the forecast factors studied

The IMDC prognostic scale currently does not fully reflect a personalized approach to prognosis in mRCC patients. It needs to be modernized and supplemented with additional prognostic factors to increase the prognostic value of the scale.

In our study, we performed Cox multivariate analysis to identify statistically significant prognostic factors affecting survival rates in mRCC patients. Using the Kaplan-Meier method, we analyzed the median OS in patients according to each prognostic factor. The results are summarized in Table 7.6.

Table 7.6 – Median OS and p of prognostic factors in mRCC patients

Favorable prognosis		
Parameters	p	Median AOD
Degree of tumor differentiation (G1-2 and G3)	<0.001	50 and 25 months
Type of metastases (synchronous and metachronous)	<0.001	22 and 40 months
Number of metastases Solitary, singular and multiple	<0.001	88 and 62 months
Visceral and non-visceral metastases	<0.001	106 and 53 months
Intermediate prognosis		
Parameters	p	Median AOD
Grades 1-2 and 3 tumor differentiation grade	0.01	64 and 39 months
Type of metastasis	<0.001	21 and 40 months
Number of metastases	<0.001	60 and 36 months
CN	0.042	41 and 22 months
Hemoglobin	0.043	42 and 28 months
ECOG status	<0.001	46 and 26 months
Visceral and non-visceral metastases	<0.001	63 and 38 months
Poor prognosis		
Parameters	p	Median AOD
Degree of differentiation	<0.001	33 and 14 months
Type of metastasis	<0.001	18 and 40 months
Hemoglobin	<0.001	31 and 12 months
ECOG status	<0.001	47 and 9 months
Number of metastases	<0.001	41 and 15 months
CN	<0.001	21 and 9 months
Metastasectomy	0.037	17 and 20 months
Visceral and non-visceral metastases	<0.001	26 and 17 months

We investigated 8 significant prognostic factors, including type and number of metastases, Fuhrman grade of tumor differentiation, hemoglobin level, ECOG status, performance of CN and metastasectomy, and presence or absence of visceral metastases.

We further categorized patients with mRCC according to prognostic factors into 3 groups (Table 7.7).

Table 7.7 – Distribution of scores in the modified prognostic model in mRCC patients

Favorable prognosis	
Parameters	Prognostic scores
Degree of tumor differentiation according to Fuhrman G1-2	0
Type of metastases (metachronous)	0
Number of metastases Solitary, single metastases	0
Hemoglobin over 100 g/L	0
ECOG 0-1	0
No visceral metastases.	1
CN (+)	1
Metastasectomy (+)	1
Intermediate prognosis	
Degree of tumor differentiation 1-2 or 3	0 or 1
Type of metastases (metachronous or synchronous)	0 or 1
Number of metastases solitary, single or multiple	0 or 1
Hemoglobin normal or less than 100 g/L	0 or 1
ECOG 0-1 or 2-4	0 or 1
Nonvisceral or visceral metastases	1 or 3
CN (±)	0 or 1
Metastasectomy (±)	0 or 1
Poor prognosis	
Degree of tumor differentiation G 3	2
Type of metastases (synchronous)	2
Number of metastases multiple	2
Hemoglobin below 100 g/L	2
ECOG 2-4	2
Visceral metastases	3
CN (-)	1
Metastasectomy (-)	1

Next, we calculated the score of prognostic factors in patients with mRCC.

The degree of tumor differentiation according to Fuhrman G1-2 – 0 points, G3 received 2 points. Depending on the time of metastases appearance, patients with synchronous metastases received 2 points, with metachronous metastases 0 points. Patients with solitary or single metastases received 0 points, and patients with multiple metastases received 2 points. Patients with normal hemoglobin were assigned 0 points and those with anemia were assigned 2 points. If visceral metastases were present, 3 points were assigned, and 1 point was assigned for nonvisceral metastases. When metastasectomy was performed, patients were assigned 0 points each, and 1 point in the absence of metastasectomy. Patients were assigned 0 points when CN was performed, and 1 point if it was not performed. Patients with ECOG 0-1 received 0 points, and with ECOG 2-4 received 2 points.

When scoring in our modified SOSh prognostic model (Semyonov, Orlova, and Shirokorad), mRCC patients were categorized into 3 prognostic groups:

0-3 points – favorable prognosis;

4-8 points is an Intermediate prognosis;

9 -15 points – poor prognosis.

The distribution of mRCC patients in the modified model according to prognostic group is presented in Table 7.8.

Table 7.8 – Distribution of mRCC patients in the modified model according to prognostic group

IMDC Forecast	Number of patients	HR
Favorable	107 (10.9)	–
Intermediate	444 (45.3)	2.24 (1.74-2.89, p<0.001)
Poor	430 (43.8)	5.82 (4.49-7.54, p<0.001)

Test	χ^2	df	p
Log-rank	277	2	<.001
Gehan	298	2	<.001
Peto-Peto	76 171	2	<.001

Thus, the favorable prognosis group in our modified model included 107 (10.9%) mRCC patients with a score of 0-3.

The intermediate prognosis group consisted of 444 patients (45.3%) with scores of 4 to 8.

The poor prognosis group included 430 (43.8%) with scores 9-15.

The prognostic score of patients in the modified SOSh model for mRCC patients was calculated by adding all the scores for individual factors. Each patient was scored from 0 to 15 points, patients were divided into 3 groups according to the prognostic score, and survival rates for each prognostic group were calculated. The Kaplan-Meier method showed that the higher the prognostic score, the lower the survival rates in mRCC patients.

Table 7.9 shows that according to the number of prognostic scores calculated 1, 3 and 5-year survival rates in mRCC patients in our modified model.

Table 7.9 – OS indicators in mRCC patients depending on the number of prognostic scores (from 0 to 15)

Prognostic scores	Number of patients	OS indicators		
		12 months	36 months	60 months
0	1	–	–	–
1	24	100%	86.5%	82%
2	37	100%	86.5%	83.6%
3	45	97.7%	90.4%	77.6%
4	80	98%	80%	49%
5	51	94%	71%	49%
6	144	94%	60%	37%
7	37	86%	56%	36%
8	135	93%	59%	22%
9	40	95%	40%	13%
10	142	83%	47%	15%
11	37	81%	23%	9%

Continuation of Table 7.9

Prognostic scores	Number of patients	IA indicators		
		12 months	36 months	60 months
12	95	64%	16%	0%
13	27	28.3%	8.1%	4%
14	61	52%	2%	0%
15	25	25%	0%	0%

For example, a patient with non-visceral metastases (1 point), anemia (2 points), ECOG quality of life 1 (0 points), solitary metastases (0 points), low-differentiated tumor (2 points), in the absence of CN (1 point) and metastasectomy (1 point) would have an overall score of 8 (1+2+0+2+1+1+1+1=8), an intermediate prognosis. This score was associated with 3- and 5-year OS of 59% and 22%.

Table 7.10 shows that according to the number of prognostic scores, the median OS of mRCC patients in our modified model ranged from 101.1 to 8 months.

Table 7.10 – Median OS in mRCC patients depending on the number of prognostic scores (0 to 15)

Prognostic scores	Number of patients	Median OS (months)
0	1	–
1	24	86 (71.5-116.6)
2	37	101.1 (72.4-109.6)
3	45	84.2 (76.9-127.2)
4	80	58.5 (46.4-77.6)
5	51	59 (51.5-75.5)
6	144	50.1 (38.5-56.1)
7	37	38.1 (29.9-71.4)
8	135	41.6 (36.7-46.3)
9	40	29.5 (21.8-45.4)
10	142	34.3 (25.4-39.7)

Continuation of Table 7.10

Prognostic scores	Number of patients	Median OS (months)
11	37	21.3 (15.6-29.8)
12	95	17.3 (14-21.2)
13	27	7.9 (6.1-24.9)
14	61	12.2 (9.7-14.7)
15	25	8 (7.4-11.9)

For example, a patient with visceral metastases (3 points), anemia (2 points), ECOG quality of life 3 (2 points), multiple metastases (2 points), low-differentiated tumor (2 points), in the absence of CN (1 point) and metastasectomy (1 point) would have a total score of 11 (3+2+2+2+2+1+1+1+1=11), a poor prognosis. This score is associated with a median OS of 21, 3 months.

Table 7.11 shows that according to the number of prognostic scores calculated 1, 3, and 5-year OS in mRCC patients in our modified model.

Table 7.11 – OS rates of mRCC patients in the 3 modified prognosis groups

Prognostic points	Survival rate, % (95% CI)		
	12 months	36 months	60 months
0-3 points	99.1 (97.3-100.0%)	88.2 (82.1-94.7%)	81 (73.6-89.1%)
4-8 points	93.6 (91.3-95.9%)	63.9 (59.4-68.7%)	35.8 (31.3-40.9%)
9-15 points	68.4 (64.1-73.1%)	25.5 (21.5-30.3%)	7.1 (4.9-10.4%)

Based on the 3 and 5-year OS scores, the following 3 groups can be distinguished (Table 7.12): a score of 3 or less corresponds to the 3 and 5-year OS scores of 88.2% and 81% (favorable prognosis group: 11% of the total population); a score of 4 to 8 corresponds to 63.9% and 35.8% (intermediate prognosis group: 45.8% of the total population); a score of 9 to 16 corresponds to the 3 and 5-year OS scores of 25.5% and 7.1% (poor prognosis group: 43.2% of the total population). Survival rates for these three groups were statistically significantly different (log-rank test, $p<0.0001$).

Table 7.12 – Median OS of mRCC patients in the 3 modified prognosis groups

Forecast	Median AOD (months)
Favorable	87.7 [77.5-104, 95% DI].
Intermediate	46.4 [43.6-51.5, 95% DI].
Poor	18.6 [16.7-21.5, 95% DI]

Thus, the median OS in mRCC patients in our modified prognostic model was 99, 46 and 19 months in the favorable, intermediate and poor prognosis groups ($p<0.0001$).

When comparing the median OB in the IMDC prognosis group and in our prognostic model, the medians were significantly different for favorable and intermediate prognosis.

The survival rates of patients with prognostic scores 0-3 (favorable prognosis group), 4-8 (intermediate prognosis group), and 9-15 (poor prognosis group) are significantly different ($p<0.0001$) (Figure 7.7).

From the analysis of Figure 7.8, it is evident that our modified prognosis model in mRCC patients showed a nonsignificant difference in terms of OS except for the favorable group.

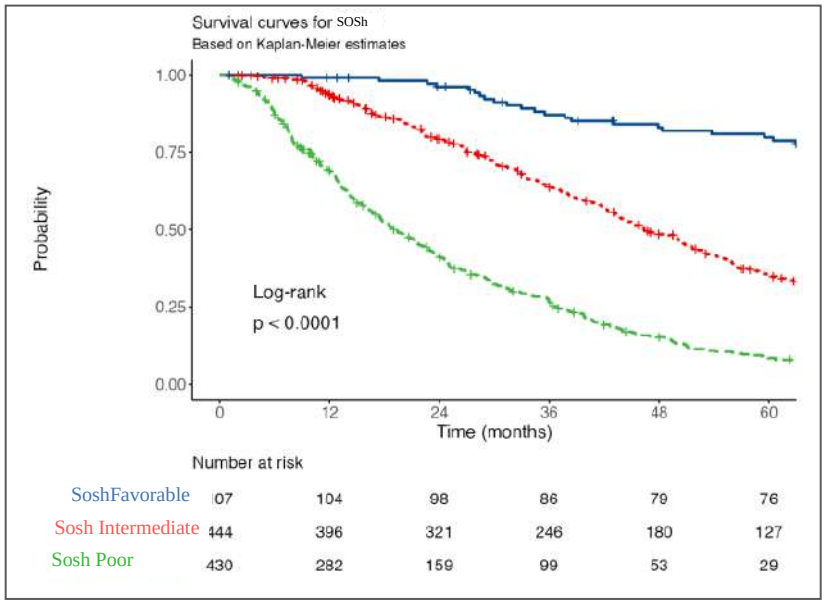

Figure 7.7 – Kaplan-Meier survival rate curves
in mRCC patients for the 3 modified prognostic groups

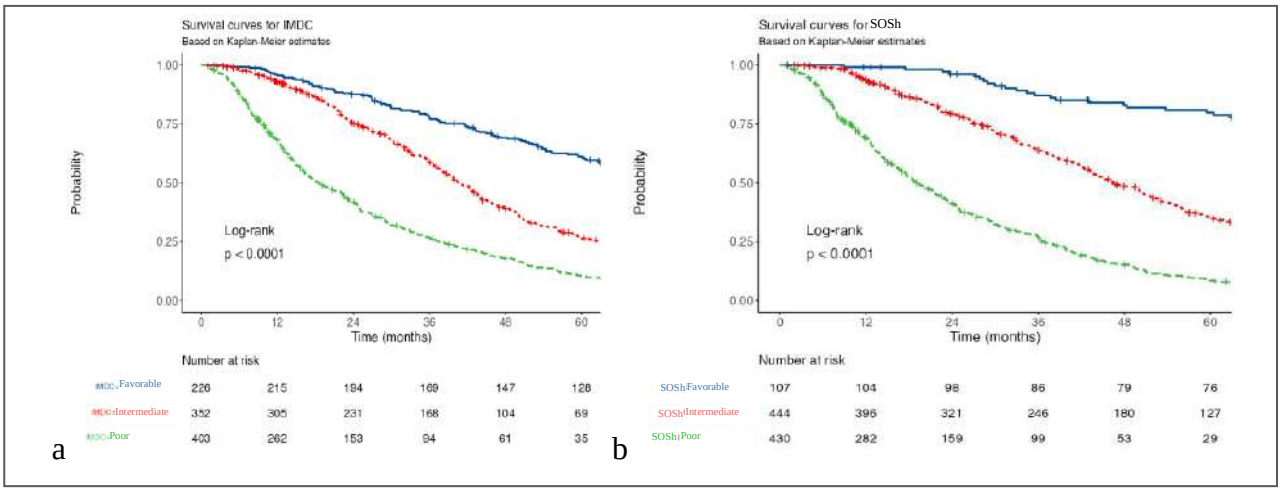

Figure 7.8 – Comparison of Kaplan-Meier curves of OS parameters in patients in IMDC prognosis groups (a) and in modified SOSh groups (b)

We also in our modified model extended the intermediate prognosis group of mRCC patients by almost 6 months. In the poor prognosis group, the OS indices did not differ among mRCC patients. Thus, this poor group, despite the inclusion of additional prognostic factors in the model, should be treated with systemic therapy with combinations of modern drugs.

Table 7.13 shows that there is no difference in survival rates in patients with poor prognosis according to IMDC and SOSh mRCC.

Table 7.13 – Comparison of 3- and 5-year OS in patients in IMDC and modified prognosis groups

Forecast	IMDC (OV%)	Modified model (OV%)
Favorable	77.4-61.1%	88.2-81%
Intermediate	58.7-26.8%	63.9-35.8%
Poor	26.6-10.4%	25.5-7.1%

Table 7.14 shows the distribution of prognostic factors in mRCC patients with favorable, intermediate, and poor prognoses by SOC.

Table 7.14 – Prognostic factors and their scoring in the modified SOSh model in mRCC patients

Prognostic factors	Favorable forecast	Intermediate forecast	Unfavorable forecast
Degree of tumor differentiation (G1-2 or G3)	0	0 or 1	2
Type of metastasis (metachronous or synchronous)	0	0 or 1	2
Number of metastases	0	0 or 1	2
Hemoglobin	0	0 or 1	2
ECOG status (0-1 or 2-4)	0		2
Nonvisceral or visceral metastases	1	1 or 3	3
CN (- or +)	1	0 or 1	2
Metastasectomy (- or +)	1	0 or 1	2

Thus, in this study, a prognostic model was built on a large material, which is applicable in real clinical practice to improve the effectiveness of treatment and survival rates of mRCC patients.

7.2.2 Study of prognostic factors in the group of unfavorable prognosis on SOSh in patients metastatic renal cell cancer and assessment of their impact on survival rates

In this group of 430 patients with poor prognosis according to SOSh, we studied the 8 prognostic factors we previously identified and their impact on survival rates in mRCC patients (Table 7.15).

Table 7.15 – Distribution of the total cohort of mRCC patients in the SOSh poor prognosis group

Prognosis	Number of patients	HR
Poor prognosis	221 (51.4)	–
Very poor prognosis	209 (48.6)	2.83 (2.28-3.50, p<0.001)

Figure 7.9 shows that in the poor prognosis subgroup (9-11 points), the 3-year and 5-year OS of patients were 42.1% [35.7-49.7%, 95% CI] and 14.4% [10.0-20.7%, 95% CI], and in the very poor prognosis subgroup (12-15 points), 9.7% [6.4-14.9%, 95% CI] and 1.0% [0.3-4.1%, 95% CI], respectively. Meanwhile, the median OS in the subgroups also differed and was 29.5 [24.6-35.9, 95% CI] and 12.4 [11-14.3, 95% CI] months, respectively. Thus, the conducted study revealed statistically significant differences in OS and median OS in subgroups of poor prognosis in patients with mRCC (p<0.0001).

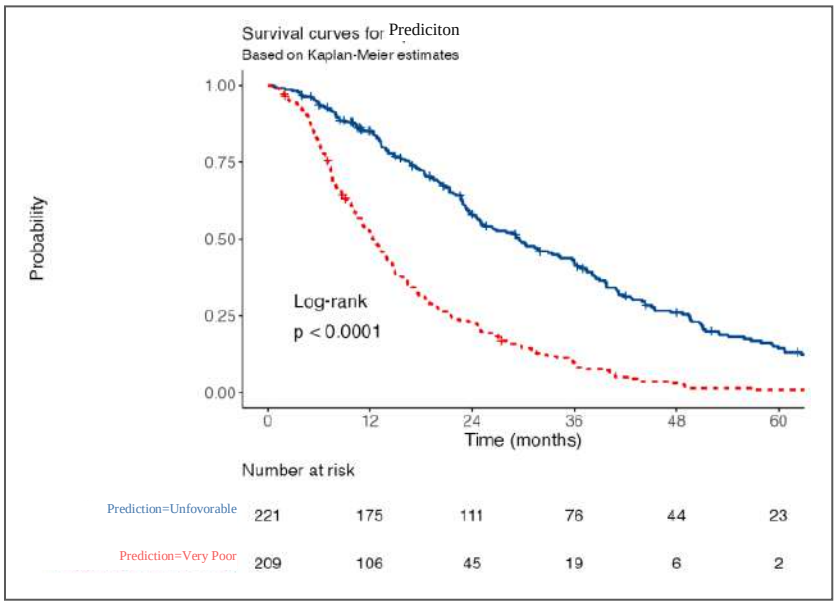

Figure 7.9 – Kaplan-Meier survival rate curves for mRCC patients with poor prognosis (N=430) for the 2 modified subgroups

The distribution of mRCC patients in the group of poor prognosis according to SOSh depending on the degree of tumor differentiation is presented in Table 7.16.

Table 7.16 – Distribution of mRCC patients in the group of poor prognosis according to SOSh depending on the degree of tumor differentiation

Degree of tumor differentiation	Number of patients	HR
G1-2	96 (22.3)	–
G3	334 (77.7)	2.83 (2.28-3.50, p<0.001)

The presented Kaplan-Meier curve diagram (Figure 7.10) shows that 3-year and 5-year OS depending on the degree of tumor differentiation at G1-2 and G3 were 38.6% [29.6-50.40%, 95% CI] and 16.7% [10.2-27.34%, 95% CI], 22.3% [18.0-27.54%, 95% CI] and 5.0% [2.9-8.34%, 95% CI], respectively. The median OS also differed between subgroups and was 28 [22.9-36.4, 95% CI] and 16.9 [14.7-19.2, 95% CI] months, respectively.

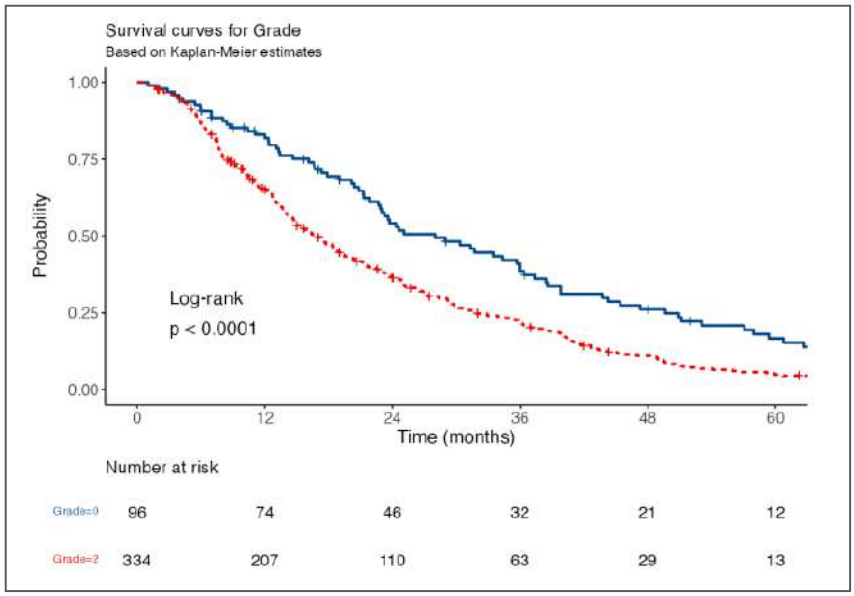

Figure 7.10 – Kaplan-Meier curves of OS indices of mRCC patients (N=430) depending on the degree of tumor differentiation according to Fuhrman in the SOSh poor prognosis group

Thus, the conducted study revealed statistically significant differences in OB and median OS in the group of poor prognosis according to SOSh in mRCC patients depending on the degree of tumor differentiation ($p<0.001$).

The distribution of mRCC patients in the SOSh poor prognosis group depending on the type of metastases is presented in Table 7.17.

The presented Kaplan-Meier curve plot (Figure 7.11) shows that the 3-year and 5-year OS rates for poor prognosis depending on metachronous and synchronous metastases were 25.0% [18.31-34.2%, 95% CI] and 9.1% [4.95-16.8%, 95% CI], 26.3% [21.57-32.2%, 95% CI] and 7.0% [4.46-11.0%, 95% CI], respectively. Meanwhile, the median OS was 18.6 [16.6-22.5, 95% CI] and 19.2 [16.1-23.2, 95% CI] months, respectively.

Table 7.17 – Distribution of mRCC patients in the group of poor prognosis according to SOSh depending on the type of metastases

Type of metastasis	Number of patients	HR
Metachronous mts	133 (30.9)	–
Synchronized mts.	297 (69.1)	1.02 (0.82-1.28, p=0.833)

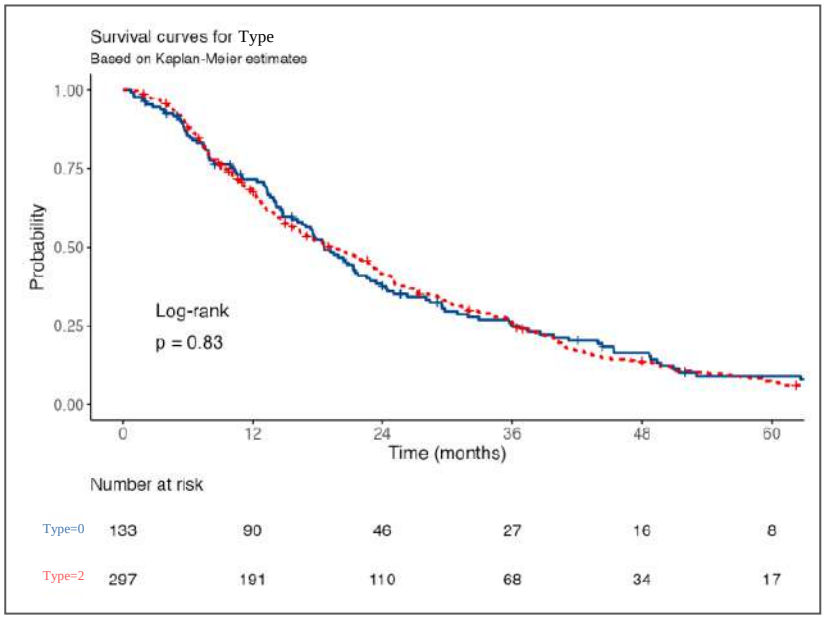

Figure 7.11 – Kaplan-Meier curves of OS indicators of mRCC patients (N=430) depending on the type of metastases in the SOSh poor prognosis group

Thus, the conducted study revealed no statistically significant differences in OS and median OS in the group of poor prognosis according to SOSh in mRCC patients depending on the type of metastases (p=0.83).

The distribution of mRCC patients in the SOSh poor prognosis group depending on the number of metastases is presented in Table 7.18.

Table 7.18 – Distribution of mRCC patients in the group of poor prognosis according to SOSh depending on the number of metastases

Number of metastases	Number of patients	HR
Solitary, single	28 (6.5)	–
Multiple	402 (93.5)	1.73 (1.14-2.63, p=0.010)

The presented Kaplan-Meier curve diagram (Figure 7.12) shows that the 3-year and 5-year OS for poor prognosis depending on the number of metastases were 54.8% [38.7-77.6%, 95% CI] and 15.6% [6.4-38.4%, 95% CI], 23.8% [19.8-28.7%, 95% CI] and 7.0% [4.7-10.4%, 95% CI] for solitary, single and multiple metastases, respectively. The median OS also differed between subgroups and was 41 [18.4-50.7, 95% CI] and 18.6 [16.4-21.3, 95% CI] months, respectively.

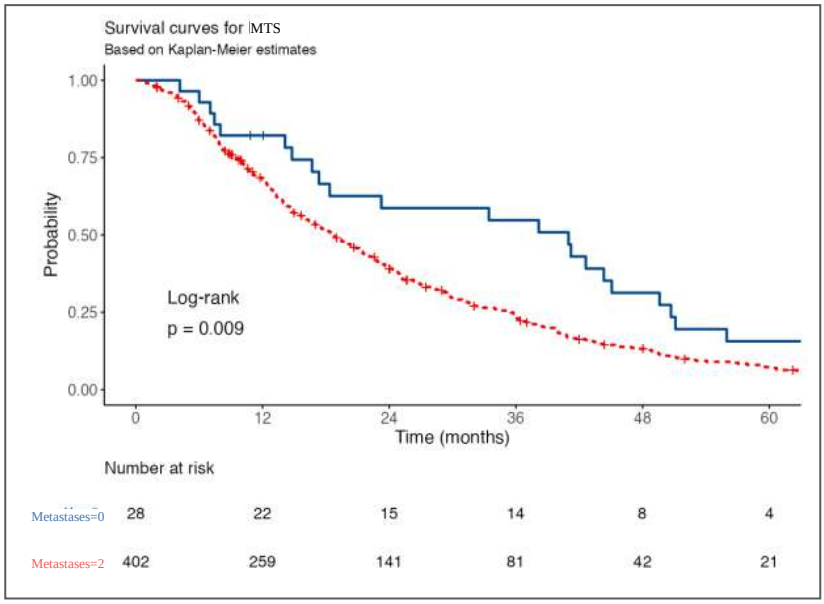

Figure 7.12 – Kaplan-Meier curves of OS indicators of mRCC patients (N=430) depending on the number of metastases in the SOSh poor prognosis group

Thus, the conducted study revealed statistically significant differences in OB and median OB in the group of poor prognosis according to SOSh in mRCC patients depending on the number of metastases (p=0.009).

The distribution of mRCC patients in the SOSh poor prognosis group depending on hemoglobin level is presented in Table 7.19.

Table 7.19 – Distribution of mRCC patients in the group of poor prognosis according to SOSh depending on hemoglobin level

Hemoglobin level	Number of patients	HR
Hemoglobin	192 (44.7)	–
Anemia	238 (55.3)	2.16 (1.75-2.65, p<0.001)

The presented Kaplan-Meier curve plot (Figure 7.13) shows that the 3-year and 5-year OS rates for poor and prognosis with hemoglobin normal and anemia were 43.2% [36.3-51.44%, 95% CI] and 10.6% [6.7-16.91%, 95% CI], 12.3% [8.7-17.45%, 95% CI] and 5.0% [2.8-9.03%, 95% CI], respectively. The median OS also differed between subgroups and was 31.1 [27.1-36.1, 95% CI] and 13.2 [12-14.8, 95% CI] months, respectively.

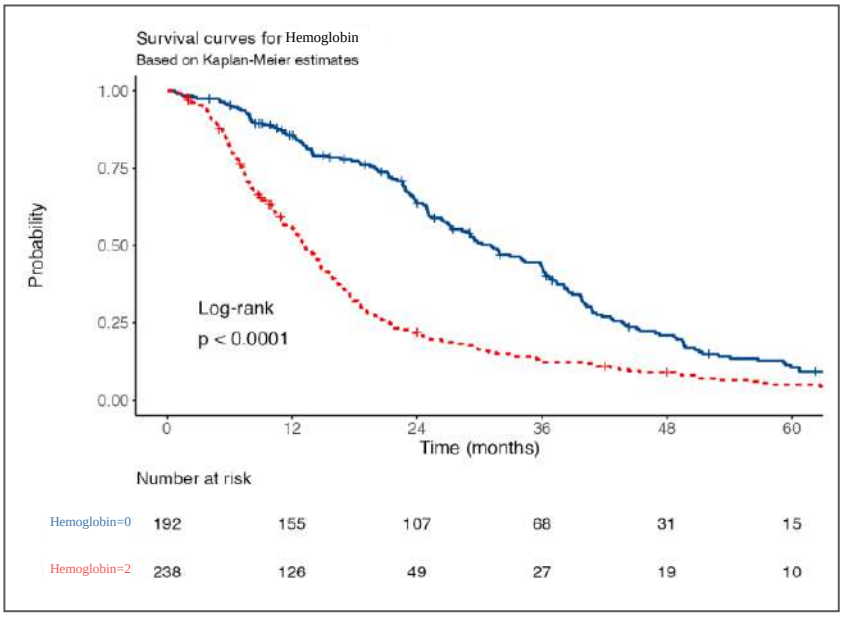

Figure 7.13 – Kaplan-Meier curves of OS indices of mRCC patients (N=430) depending on hemoglobin level in the SOSh poor prognosis group

Thus, the conducted study revealed statistically significant differences in OB and median OB in the group of poor prognosis according to SOSh in mRCC patients depending on hemoglobin level ($p<0.0001$).

The distribution of mRCC patients in the SOSh poor prognosis group depending on ECOG status is presented in Table 7.20.

Table 7.20 – Distribution of mRCC patients in the group of poor prognosis according to SOSh depending on ECOG status

ECOG status	Number of patients	HR
ECOG 0-1	62 (14.4)	–
ECOG 2-3	368 (85.6)	2.42 (1.70-3.45, $p<0.001$)

The presented Kaplan-Meier curve plot (Figure 7.14) shows that the 3-year and 5-year OS rates for poor prognosis depending on ECOG status were 56.9% [43.9-73.6%, 95% CI] and 24.3% [13.2-44.8%, 95% CI], 21.9% [17.9-26.7%, 95% CI] and 5.5% [3.5-8.6%, 95% CI]respectively. Meanwhile, the median OS in the subgroups also differed and was 41 [29.1-59.2, 95% CI] and 17.3 [14.9-20, 95% CI] months, respectively. Thus, the study revealed statistically significant differences in OS and median OS in the group of poor prognosis by SOSh in mRCC patients depending on ECOG status (p<0.0001).

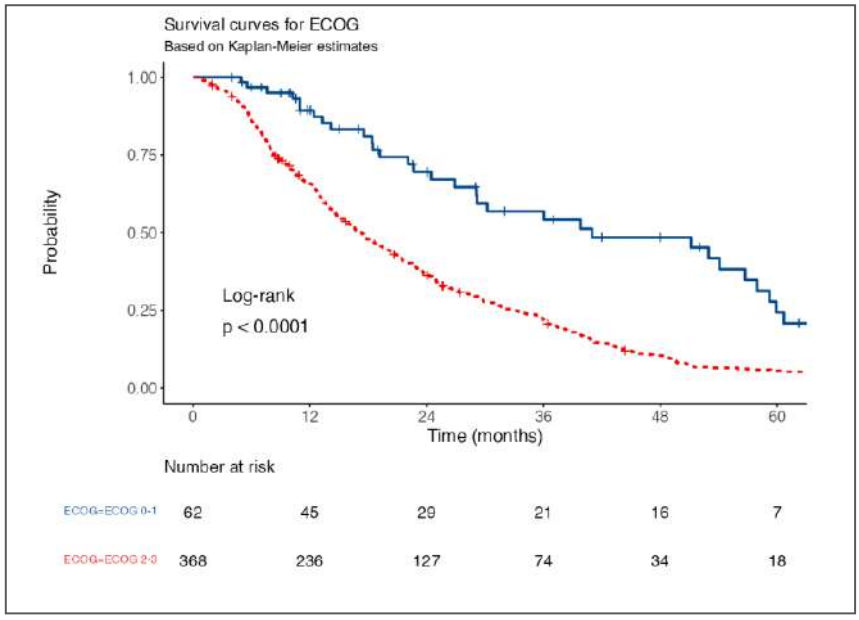

Figure 7.14 – Kaplan-Meier curves of OS indicators of mRCC patients (N=430) depending on ECOG status in the SOSh poor prognosis group

The distribution of mRCC patients in the SOSh poor prognosis group depending on the presence of nonvisceral and visceral metastases is presented in Table 7.21.

The presented Kaplan-Meier curve plot (Figure 7.15) shows that the 3-year and 5-year OS rates for poor prognosis depending on the presence of nonvisceral and visceral metastases were 23.4% [13.1-41.8%, 95% CI] and 5.8% [1.5-22.2%, 95% CI], 26.2% [22.0-31.2%, 95% CI] and 7.8% [5.3-11.4%, 95% CI], respectively. Meanwhile, the median OS was 18.4 [12.5-26.5, 95% CI] and 19.2 [16.9-22.1, 95% CI] months, respectively.

Table 7.21 – Distribution of mRCC patients in the group of poor prognosis according to SOSh depending on the presence of nonvisceral and visceral metastases

Non-visceral/visceral mts	Number of patients	HR
Nonvisceral metastases	42 (9.8)	–
Visceral metastases	388 (90.2)	0.91 (0.65-1.27, p=0.574)

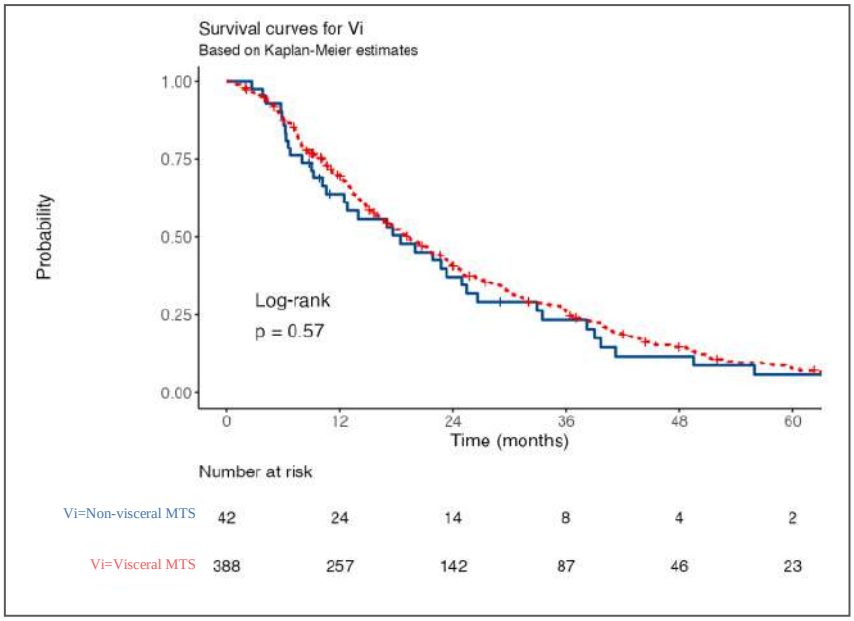

Figure 7.15 – Kaplan-Meier curves of OS indices of mRCC patients (N=430) depending on the presence of nonvisceral and visceral metastases in the SOSh poor prognosis group

Thus, the study did not reveal statistically significant differences in OS and median OS in the group of p poor rognosis according to SOSh in mRCC patients depending on the presence of non-visceral and visceral metastases (p=0.57).

In our earlier study, the survival rates of mRCC patients (N=330) in IMDC prognostic groups when performing CN are demonstrated in Figure 7.16.

The OS rates in the poor prognosis group when evaluated by IMDC of mRCC patients were 31.08% [25.4-38.00%, 95% CI] and 12.64% [8.8-18.15%, 95% CI], respectively.

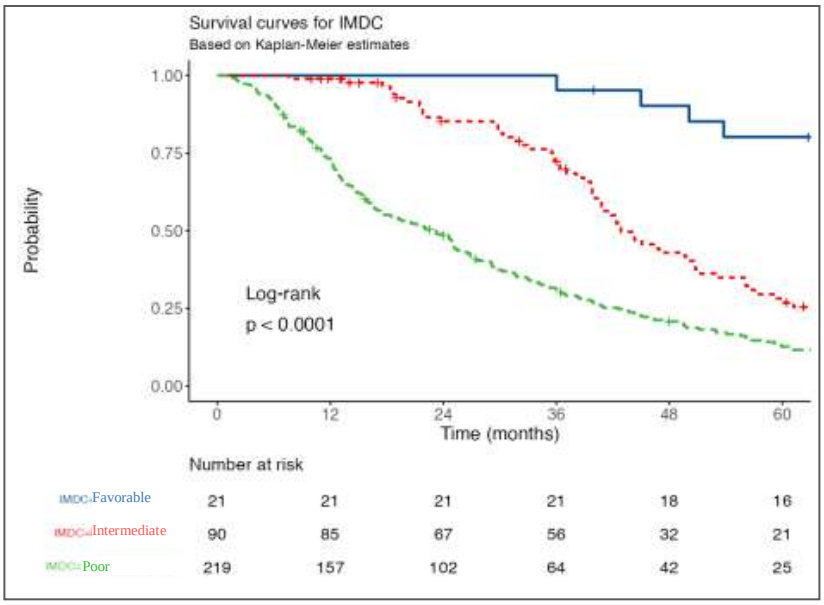

Figure 7.16 – Distribution of mRCC patients (N=330) when performing CN depending on the IMDC forecast

In our study, we investigated the effect of cytoreductive surgery on survival rates in mRCC patients with poor prognosis according to SOSh.

Table 7.22 shows that 73 (17%) patients in the SOSh poor prognosis group CN was not performed.

Table 7.22 – Distribution of mRCC patients in the group of poor prognosis according to SOSh depending on CN performance

CN	Number of patients	HR
CN (+)	357 (83.0)	–
CN (-)	73 (17.0)	1.82 (1.37-2.40, p<0.001)

The presented Kaplan-Meier curve plot (Figure 7.17) shows that the 3-year and 5-year OS rates for poor prognosis depending on CN performance were 28.8% [24.3-34.2%, 95% CI] and 8.2% [5.6-12.0%, 95% CI], 9.5% [4.2-21.6%, 95% CI] and 3.8% [1.0-14.7%, 95% CI], respectively. Meanwhile, the median OS also differed and was 20.6 [18.4-24, 95% CI] and 10.1 [8-14.3, 95% CI] months, respectively.

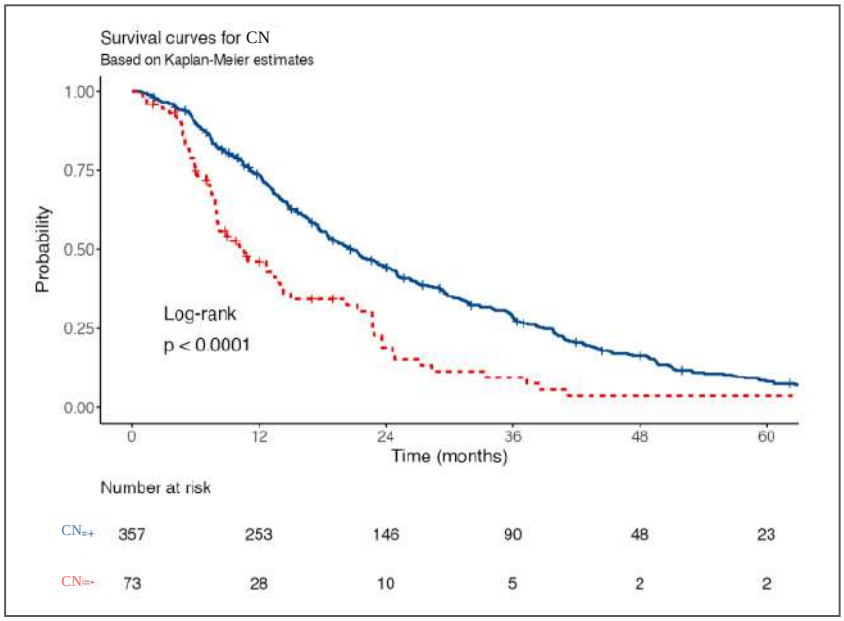

Figure 7.17 – Kaplan-Meier curves of OS indicators of mRCC patients (N=430) depending on CN performance in the SOSh poor prognosis group

Thus, the conducted study revealed statistically significant differences in OS and median OS in the group of poor prognosis according to SOSh in mRCC patients depending on the performance of CN ($p<0.0001$).

We compared the survival rates of mRCC patients with poor prognosis in the IMDC model and the modified SOSh model when performing CN, which are presented in Table 7.23.

Table 7.23 – Survival rates of patients with poor prognosis of mRCC when performing CN

OS indicators	poor prognosis IMDC	poor prognosis SOSh
3-year OS	31.0%	28.8%
5-year OS	12.6%	8.2%

Table 7.23 shows that there is no statistically significant difference in survival rates in mRCC patients with poor prognosis in the IMDC model and modified SOSh model when performing CN.

Thus, performing CN is reasonable in mRCC patients of poor prognosis according to SOSh ($p<0.0001$).

In our earlier study, the survival rates of mRCC patients (N=226) in IMDC prognostic groups when metastasectomy was performed are demonstrated in Figure 7.18.

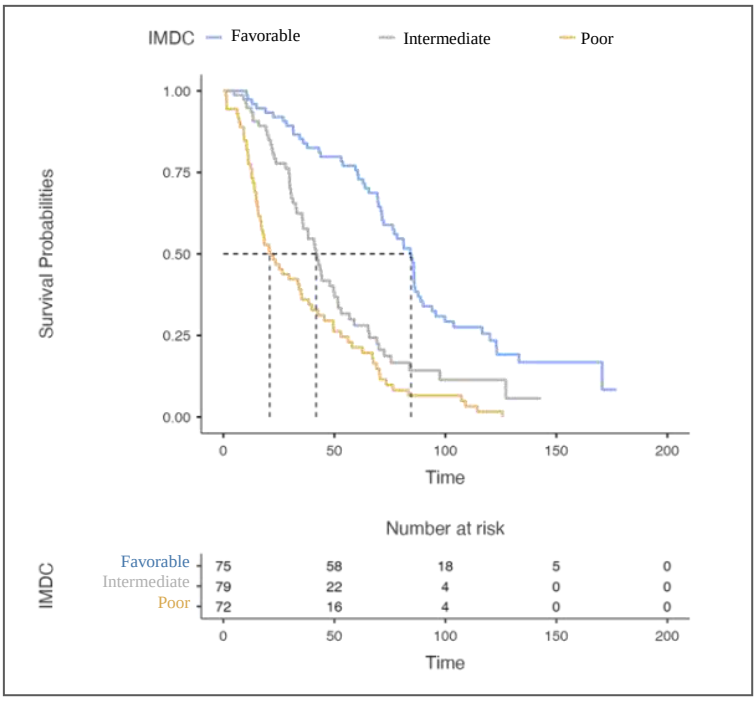

Figure 7.18 – Distribution of mRCC patients
when performing metastasectomy depending on IMDC prognosis

Figure 7.18 shows that the OS rates in the poor prognosis group when evaluated by IMDC when metastasectomy was performed were 36.0% [26.2-49.54%, 95% CI] and 21.3% [13.3-34.16%, 95% CI], respectively.

When we analyzed survival rates in our modified model, we obtained the following results.

Table 7.24 shows that 70 (16.3%) patients in the SOSh poor prognosis group underwent metastasectomy.

Table 7.24 – Distribution of mRCC patients in the group of poor prognosis according to SOSh depending on the metastasectomy performed

Metastasectomy	Number of patients	HR
Metastasectomy (+)	70 (16.3)	–
Metastasectomy (-)	360 (83.7)	1.22 (0.94-1.60, p=0.140)

The presented Kaplan-Meier curve plot (Figure 7.19) shows that the 3-year and 5-year OS rates for poor prognosis depending on whether or not metastasectomy was performed were 29.3% [20.14-42.5%, 95% CI] and 12.1% [6.28-23.4%, 95% CI], 25.3% [20.94-30.5%, 95% CI] and 6.6% [4.28-10.2%, 95% CI], respectively. Meanwhile, the median OS was 41 [22.9 [18.4-31.3, 95% CI] and 18.4 [16.1-21.5, 95% CI] months, respectively.

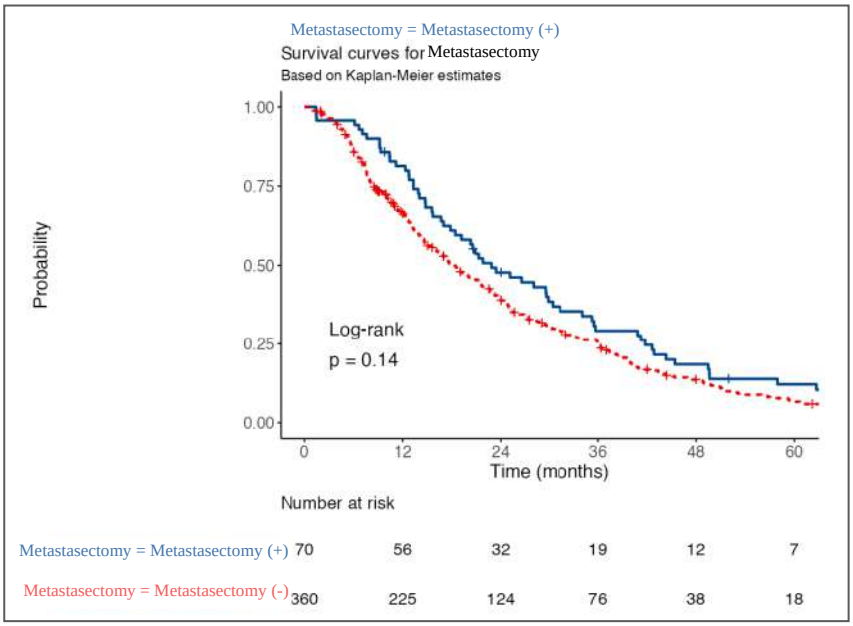

Figure 7.19 – Kaplan-Meier curves of OS indices of mRCC patients (N=430) depending on the performance of metastasectomy in the SOSh poor prognosis group

Thus, the study showed no statistically significant differences in the OS and median OS in the group of poor prognosis according to SOSh in mRCC patients depending on the performance of metastasectomy (p=0.14).

We compared the survival rates of mRCC patients with poor prognosis in the IMDC model and the modified SOSh model when metastasectomy was performed, which are presented in Table 7.25.

Table 7.25 – Survival rates of poor prognosis mRCC patients when metastasectomy is performed

OS indicators	poor prognosis IMDC	poor prognosis SOSh
3-year OS	36.0%	29.3%
5-year OS	21.3%	12.1%

Table 7.25 shows that there is no statistically significant difference in survival rates in mRCC patients with poor prognosis in the IMDC model and modified SOSh model when metastasectomy is performed.

Thus, the conducted study revealed statistically significant differences in OB and median OB in the group of poor prognosis according to SOSh in mRCC patients depending on the performance of CN ($p<0.0001$), but not metastasectomy ($p=0.14$).

Thus, statistically significant differences were found for 5 factors out of 8 prognostic factors when analyzing the OB indices based on Kaplan-Meier curves in mRCC patients. The conducted study revealed statistically significant differences in OS and median OS in the group of poor prognosis according to SOSh in patients with mRCC depending on the degree of tumor differentiation, number of metastases, ECOG status, hemoglobin level, and NE performance.

Next, in our study of the group of patients with poor prognosis according to SOSh, we performed single- and multivariate Cox analysis. The data are presented in Table 7.26.

Table 7.26 – Cox proportional hazards model of the effect of the SOSh model (N=430) on OS outcomes in the group of mRCC patients with a poor prognosis

Factors	Gradations	Number of patients	HR (single-factor)	HR (multivariate)
CN	CN (+)	357 (83.0)	–	–
	CN (-)	73 (17.0)	1.82 (1.37-2.40, p<0.001)	1.66 (1.22-2.26, p=0.001)
Degree of differentiation tumors	G1-2	96 (22.3)	–	–
	3	334 (77.7)	1.67 (1.30-2.15, p<0.001)	1.84 (1.32-2.56, p<0.001)
Type of metastasis	metachronous mts	133 (30.9)	–	–
	synchronous mts	297 (69.1)	1.02 (0.82-1.28, p=0.833)	1.31 (1.00-1.73, p=0.049)
	nonvisceral mts	42 (9.8)	–	–
	visceral mts	388 (90.2)	0.91 (0.65-1.27, p=0.574)	0.95 (0.64-1.39, p=0.780)
Number Metastasis	solitary, single	28 (6.5)	–	–
	multiple	402 (93.5)	1.73 (1.14-2.63, p=0.010)	2.46 (1.48-4.09, p<0.001)
Hemoglobin	hemoglobin normally	192 (44.7)	–	–
	anemia	238 (55.3)	2.16 (1.75-2.65, p<0.001)	2.45 (1.86-3.21, p<0.001)
ECOG	ECOG 0-1	62 (14.4)	–	–
	ECOG 2-3	368 (85.6)	2.42 (1.70-3.45, p<0.001)	3.08 (2.00-4.73, p<0.001)
Metastasectomy	0	70 (16.3)	–	–
	1	360 (83.7)	1.22 (0.94-1.60, p=0.140)	1.50 (1.12-2.03, p=0.007)

As shown in Table 7.26, in the single- and multivariate analysis, the degree of tumor differentiation, number and type of metastases, ECOG status, hemoglobin level, and CN performance were additional factors influencing OS in mRCC patients with poor prognosis according to SOSh.

Thus, in our modified SOSh model in patients with poor prognosis, we studied 8 prognostic factors and their impact on survival rates in mRCC patients. Further analysis revealed statistically significant differences in OS and median OS in the SOSh poor prognosis group in mRCC patients ($p<0.0001$). In single- and multivariate analysis, the degree of tumor differentiation, number of metastases, ECOG status, hemoglobin level, and performance of HE were additional factors influencing the RR in mRCC patients with poor prognosis according to SOSh. Thus, in our opinion, there is a need not only to modernize the IMDC prognostic model, but also a clearer picture of the heterogeneous group of poor prognosis of mRCC patients. This is necessary for a more effective approach to personalized systemic therapy in mRCC patients.

7.3 Study of cytoreductive surgical interventions on survival rates in the unfavorable group and very unfavorable prognosis according to SOSh in patients with metastatic renal cell cancer

7.3.1 Effect of cytoreductive nephrectomy on indices of survival in subgroups with unfavorable prognosis by SOSh

At present, there is no clear consensus among researchers whether it is necessary to perform CN in poor prognosis mRCC patients under systemic therapy [77, 79]. The group of poor prognosis with high metastatic load is heterogeneous. In our study, we found that there is no difference in survival rates in mRCC patients with poor prognosis based not only on the IMDC model but also on our modified

SOSh model. Therefore, we decided to divide the group of poor prognosis of the modified model of mRCC patients into 2 subgroups: the group of poor and very poor prognosis and to study the effect of cytoreductive surgeries on survival rates.

The first group of opoor prognosis included mRCC patients with a score of 9-11, and the very poor prognosis group included patients with a score of 12-15 on our modified SOSh scale.

7.3.2 Effect of cytoreductive nephrectomy on indices of survivalin subgroups with unfavorable prognosis by SOSh in patients with metastatic renal cell disease cancer

We compared the survival rates of mRCC patients with poor prognosis in two subgroups of the modified SOSh model when performing CN, the graphs are presented in Figure 7.20.

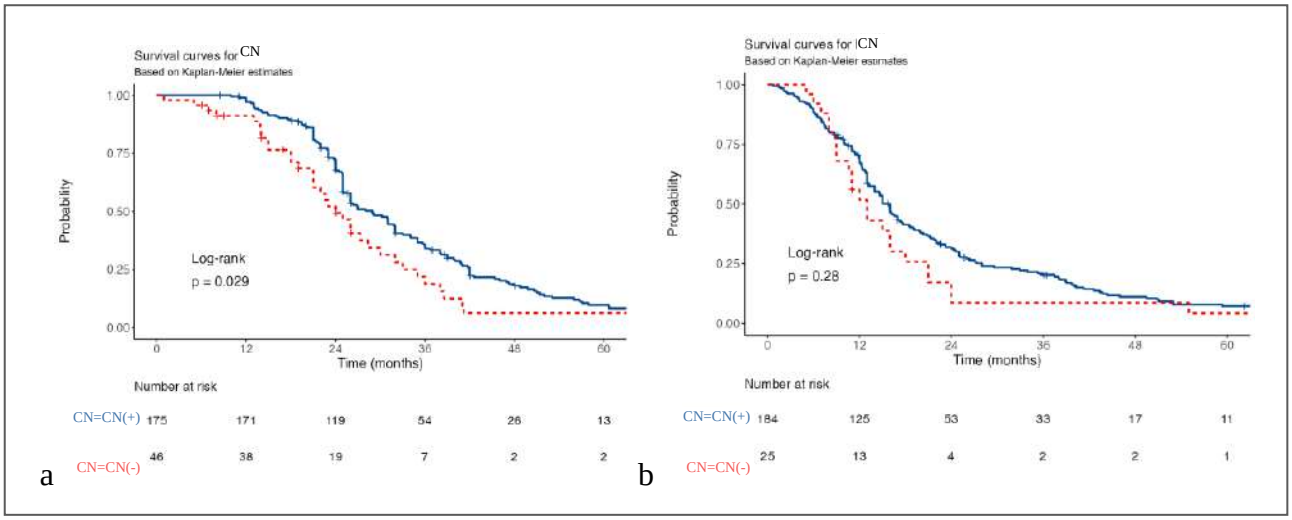

Figure 7.20 – Kaplan-Meier curves of OS indicators in mRCC patients when performing CN in the subgroups with poor prognosis (a) and very poor prognosis (b) by SOSh

The presented Kaplan-Meier curve plot shows that the 3-year and 5-year OS rates for poor depending on CN performance were 34.0% [27.4-42.25%, 95% CI] and 9.8% [5.9-16.13%, 95% CI], 18.8% [9.3-37.95%, 95% CI] and 6.3% [1.6-23.71%, 95% CI], and for very poor prognosis 20.3% [15.1-27.38%, 95% CI] and 7.2% [4.1-12.63%, 95% CI], 8.6% [2.3-32.29%, 95% CI] and 4.3% [0.6-29.23%, 95% CI], respectively. Meanwhile, the median OS in the subgroups was 29 [26-32, 95% CI] and 24 [21-32, 95% CI], 15.9 [14-17.5, 95% CI] and 13 [10.6-21, 95% CI] months, respectively.

Thus, the study revealed statistically significant differences in OS rates in the subgroup of poor prognosis in mRCC patients depending on the performance of CN (p=0.02), but not in the subgroup of very poor prognosis (p=0.28).

7.3.3 Effect of metastasectomy on survival rates in subgroups of unfavorable prognosis according to SOSh in patients with metastatic renal cell cancer

We compared survival rates of mRCC patients with poor prognosis in two subgroups of the modified SOSh model when metastasectomy was performed, the graphs are presented in Figure 7.21.

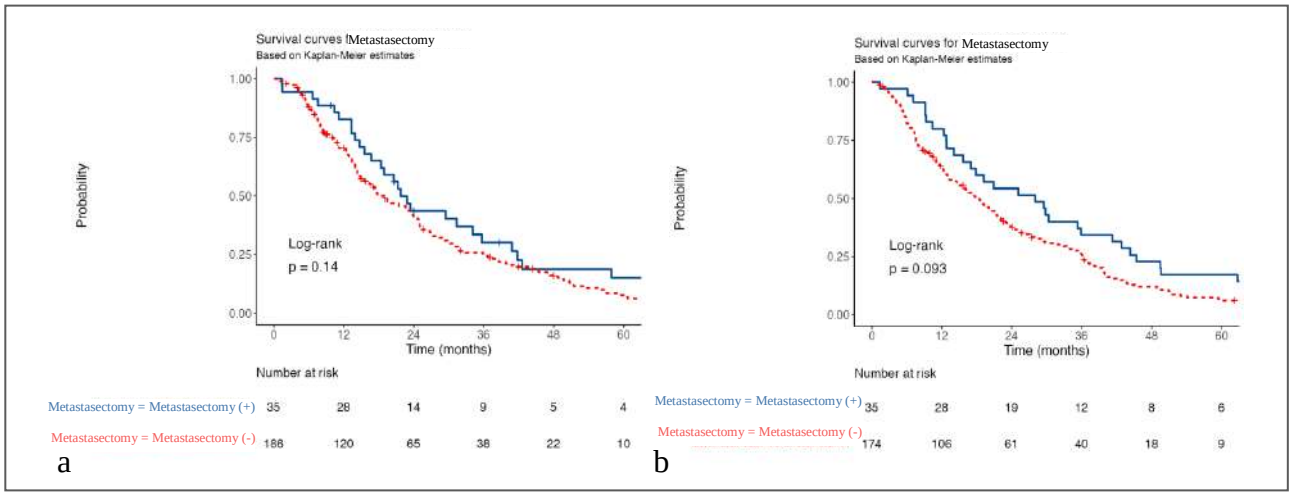

Figure 7.21 – Kaplan-Meier curves of OS indicators of mRCC patients (N=430) depending on the metastasectomy performed in poor prognosis subgroups (a) and very poor prognosis (b) by SOSh

The presented Kaplan-Meier curve plot shows that the 3-year and 5-year OS rates for poor prognosis depending on the metastasectomy performed were 30,2% [17.8-51.3%, 95% CI] and 15.1% [6.3-36.1%, 95% CI], 25.2% [19.3-32.8%, 95% CI] and 7.7% [4.3-13.7%, 95% CI], and for very poor prognosis 34.3% [21.7-54.2%, 95% CI] and 17.1% [8.3-35.5%, 95% CI], 26.2% [20.2-33.9%, 95% CI] and 6.1% [3.2-11.4%, 95% CI], respectively. Meanwhile, the median OS was 21.8 [18.4-40.9, 95% CI] and 18.9 [15.5-24, 95% CI], 28 [17-42.9, 9% CI] and 18.5 [14.6-21.7, 95% CI] months, respectively.

Thus, the study showed no statistically significant differences in OB rates in subgroups of poor prognosis in mRCC patients depending on the performance of metastasectomy (p=0.114 and p=0.093).

As a result of studying the effect of CN on survival rates in patients with poor prognosis of the modified SOSh model, we clearly showed that performing CN is inappropriate in patients with very poor prognosis according to SOSh (p=0.28). In our study, we found no difference in survival rates in mRCC patients of poor and very poor prognosis according to SOSh when performing metastasectomy (p=0.114 and p=0.093).

7.4 Characterization and efficiency of the first and second lines systemic therapy in patients with metastatic renal-lethal cancer according to prognosis in the modified SOSh model and comparison with IMDC prognosis groups

7.4.1 Characterization and efficacy of 1 line of systemic therapy in patients with metastatic renal cell cancer depending on the forecast in the modified model SOSh and comparison with IMDC prediction groups

In our study, we further investigated the application value of the modified SOSh model with respect to the outcomes of 1st line systemic therapy in mRCC patients according to prognosis groups.

In the first-line setting, all 981 patients received different types of systemic treatment. We examined the response rate to first-line systemic therapy in mRCC patients according to IMDC and SOSh prognosis groups, and the group distribution is presented in Tables 7.27-7.33.

Table 7.27 – Distribution of mRCC patients in IMDC and SOSh prognosis groups for systemic therapy in the 1st line of therapy

Forecast groups	Targeted therapy		Immunotherapy	
	IMDC number of patients (n=774) %	SOSh number of patients (n=774) %	IMDC number of patients (n=59) %	SOSh number of patients (n=64) %
Favorable	166	67	19	21
Intermediate	269	347	18	19
Poor	339	360	22	24
Poor/ Very poor	0	174/186	0	11/13

Table 7.28 – Comparison of responses in mRCC patients with favorable prognosis according to IMDC and SOSh with 1st line targeting therapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	TKI (n=166)	TKI (n=67)	
Complete response	2 (1.2%)	2 (3%)	chi^2=0.89, p=0.34
Partial response	16 (9.6%)	7 (10.4%)	chi^2=0.03, p=0.85
Stabilization	95 (57.2%)	41 (61.2%)	chi^2=0.89, p=0.34
Progression	53 (32%)	17 (25.4%)	chi^2=0.97, p=0.32

Table 7.29 – Comparison of responses in mRCC patients of intermediate prognosis according to IMDC and SOSh with 1st line targeting therapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	TKI (n=269)	TKI (n=347)	
Complete response	7 (2.6%)	6 (1.7%)	chi^2=0.89, p=0.34
Partial response	24 (8.9%)	32 (9.2%)	chi^2=0.02, p=0.86
Stabilization	124 (46.1%)	171 (49.3%)	chi^2=0.61, p=0.43
Progression	114 (42.4%)	138 (39.8%)	chi^2=0.42, p=0.51

Table 7.30 – Comparison of responses in mRCC patients with poor prognosis according to IMDC and SOSh with 1st line targeting therapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	TKI (n=339)	TKI (n=360)	
Complete response	–	2 (0.6%)	chi^2=0.89, p=0.34
Partial response	28 (8.2%)	29 (8.0%)	chi^2=0.28, p=0.59
Stabilization	117 (34.5%)	123 (34.2%)	chi^2=0.0093, p=0.92
Progression	194 (57.3%)	206 (57.2%)	chi^2=0, p=0.99

Thus, in our study, we observed no difference in response to 1st-line therapies in patients with mRCC depending on prognosis in the modified SOSh and IMDC model.

Table 7.31 – Comparison of responses in mRCC patients with a favorable prognosis according to IMDC and SOSh with 1st line immunotherapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	ICI (n=19)	ICI (n=21)	
Complete response	1 (5.2%)	1 (4.8%)	chi^2=0.00, p=0.94
Partial response	2 (10.5%)	3 (14.2%)	chi^2=0.22, p=0.63
Stabilization	10 (52.7%)	11 (52.3%)	chi^2=0.0003, p=0.98
Progression	6 (31.6%)	6 (28.5%)	chi^2=0.043, p=0.83

Table 7.32 – Comparison of responses in mRCC patients of intermediate prognosis according to IMDC and SOSh with 1st line immunotherapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	ICI (n=18)	ICI (n=19)	
Complete response	1 (5.5%)	2 (3%)	chi^2=0.30, p=0.57
Partial response	1 (5.5%)	2 (3%)	chi^2=0.30, p=0.57
Stabilization	6 (33.3.0%)	13 (68.4%)	chi^2=4.55, p=0.032
Progression	10 (55.0%)	3 (15.8%)	chi^2=6.41, p=0.011

Table 7.33 – Comparison of responses in IMDC and SOSh poor prognosis mRCC patients with 1st line immunotherapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	ICI (n=22)	ICI (n=24)	
Complete response	1 (4.5%)	2 (8.3%)	chi^2=0.27, p=0.60
Partial response	1 (4.5%)	2 (8.3%)	chi^2=0.004, p=0.94
Stabilization	7 (31.8%)	15 (62.5%)	chi^2=4.33, p=0.037
Progression	13 (59.1%)	5 (20.8%)	chi^2=7.5, p=0.0079

Thus, with 1st line systemic therapy in mRCC patients in the IMDC and modified SOSh prognosis groups, there was a difference in response in patients with intermediate (p=0.032 and p=0.011) and poor SOSh prognosis (p=0.037 and p=0.0079) when immunotherapy was used.

7.4.2 Characterization and efficacy of 2 lines of systemic therapy in patients with metastatic renal cell cancer depending on the forecast in the modified model SOSh and comparison with IMDC prediction groups

In our study, we further investigated the application value of the modified SOSh model with respect to the outcomes of 2nd line systemic therapy in mRCC patients according to prognosis groups.

We reviewed the response rate to 2nd line systemic therapy in mRCC patients according to IMDC and SOSh prognosis groups, the group distribution is presented in Tables 7.34-7.40.

Table 7.34 – Distribution of mRCC patients in IMDC and SOSh prognosis groups for 2-line systemic therapy

Forecast groups	Targeted therapy		Immunotherapy	
	IMDC number of patients (n=484) %	SOSh number of patients (n=391) %	IMDC number of patients (n=52) %	SOSh number of patients (n=56) %
Favorable	123	42	16	17
Intermediate	191	218	16	18
Poor	170	173	20	21
Poor/ Very poor	0	85/88	0	10/11

Table 7.35 – Comparison of responses in mRCC patients with a favorable prognosis according to IMDC and SOSh with 2-line targeted therapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	TKI (n=123)	TKI (n=42)	
Complete response	–	–	–
Partial response	15 (12.2%)	5 (11.9%)	chi^2=0.004, p=0.94
Stabilization	68 (55.3%)	22 (53.4%)	chi^2=0.1065, p=0.744
Progression	40 (32.5%)	15 (35.7%)	chi^2=0.143, p=0.704

Table 7.36 – Comparison of responses in mRCC patients of intermediate prognosis according to IMDC and SOSh with 2nd line targeting therapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	TKI (n=191)	TKI (n=218)	
Complete response	–	–	–
Partial response	10 (5.2%)	9 (4.1%)	chi^2=0.28, p=0.59
Stabilization	97 (50.8%)	124 (56.9%)	chi^2=3.1, p=0.077
Progression	84 (44%)	85 (39.0%)	chi^2=1.04, p=0.306

Table 7.37 – Comparison of responses in mRCC patients with unfavorable prognosis according to IMDC and SOSh with 2nd line targeting therapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	TKI (n=170)	TKI (n=173)	
Complete response	–	–	–
Partial response	2 (1.2%)	7 (4.1%)	chi^2=0.64, p=0.42
Stabilization	67 (39.4%)	91 (52.6%)	chi^2=6.003, p=0.014
Progression	101 (59.4%)	75 (43.3%)	chi^2=8.85, p=0.003

In summary, our study noted a difference in response to 2nd line therapies in patients with poor prognosis mRCC in the modified SOSh model (p=0.014 and p=0.003).

Table 7.38 – Comparison of responses in mRCC patients with favorable prognosis according to IMDC and SOSh with 2nd line immunotherapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	ICI (n=16)	ICI (n=17)	
Complete response	–	–	–
Partial response	1 (6.2%)	2 (11.8%)	chi^2=0.30, p=0.58
Stabilization	7 (43.8%)	7 (41.2%)	chi^2=0.02, p=0.88
Progression	8 (50%)	8 (47.0%)	chi^2=0.02, p=0.86

Table 7.39 – Comparison of responses in mRCC patients of intermediate prognosis according to IMDC and SOSh with 2nd line immunotherapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	ICI (n=16)	ICI (n=18)	
Complete response	–	1 (5,6%)	–
Partial response	1 (6.2%)	1 (5.6%)	chi^2=0.0074, p=0.93
Stabilization	5 (31.25%)	12 (66.7%)	chi^2=4.25, p=0.039
Progression	10 (50%)	4 (22.2%)	chi^2=5.67, p=0.017

Table 7.40 – Comparison of responses in mRCC patients with poor prognosis according to IMDC and SOSh with 2nd line immunotherapy

Response to therapy	IMDC number of patients (n=) %	SOSh number of patients (n=) %	chi-square, p-value (df=1)
	ICI (n=20)	ICI (n=21)	
Complete response	–	1 (4.8%)	–
Partial response	1 (5.0%)	1 (4.8%)	chi^2=0.0074, p=0.93
Stabilization	7 (35.0%)	14 (66.7%)	chi^2=4.10, p=0.042
Progression	12 (60%)	6 (28.5%)	chi^2=4.01, p=0.042

Thus, when systemic therapy of 2 lines in mRCC patients in IMDC and modified SOSh prognosis groups, there was a difference in responses in patients with poor prognosis according to SOSh in case of target therapy (p=0,014 and p=0.003), with the use of immunotherapy in first and second line intermediate (p=0.032 and p=0.011), (p=0.039 and p=0.017) and poor prognosis according to SOSh (p=0.037 and p=0.0079), (p=0.042 and p=0.042).

Conclusion

Over the last decade, modern immunotherapy has transformed treatment efficacy and improved survival rates in mRCC patients, which makes it necessary to reconsider the prognostic stratification of prognosis based on the model developed by Heng in the TKI era. No personalized models of patient survival have been developed taking into account extended prognostic factors, no data on the presence of visceral crisis are available, and clinical, laboratory and pathomorphological parameters are not taken into account. Currently, the choice of therapy for mRCC is strictly based on the developed factors, but they include few parameters. It is necessary to expand the panel of prognostic factors for a personalized approach in the treatment of mRCC.

Based on the clinical, laboratory, and pathomorphologic study of mRCC patients, we created a logistic regression model for predicting the 5-year OS

of mRCC patients and evaluated it using ROC analysis. The obtained logistic regression model for predicting the 5-year OS using the 4 most significant predictor factors was statistically significant ($p<0.001$) and 93.3% classifiable. The sensitivity of the model was 98.3% and specificity was 62.3%.

In our study, we modified the score system for assessing the prognosis of patients with mRCC depending on 8 independent prognostic factors, including the type and number of metastases, the degree of tumor differentiation according to Fuhrman, hemoglobin level, ECOG status, CN and metastasectomy, and the presence or absence of visceral metastases. In our study we divided mRCC patients depending on our additional prognostic factors into 3 groups of favorable, intermediate and unfavorable prognosis. Thus favorable prognosis corresponds to 0 to 3 points, moderate prognosis to 4 to 8 points, and poor prognosis to 9 to 15 points, respectively. The modified SOSh prognosis scoring model differs from the existing (International Metastatic Renal Cell Carcinoma Database Consortium) IMDC [32] by the increased number of evaluated prognostic factors, which in turn can lead to an increase in the sensitivity and specificity of the new scale and improve the effectiveness of treatment and survival rates in patients with mRCC. The 5-year OS rates in the modified SOSh prognosis groups were 81% (73.6-89.1%), 35.8% (31.3-40.9%), and 7.1% (4.9-10.4%), respectively ($p<0.0001$).

In a modified SOSh model in the unfavorable prognosis group, we studied prognostic factors in mRCC patients and evaluated their influence on survival rates. In single- and multivariate analysis, the degree of tumor differentiation, type and number of metastases, ECOG status, hemoglobin level and performance of metastasectomy and CN were additional factors influencing the survival rates in mRCC patients with poor prognosis according to SOSh. In our opinion, there is a need to study a heterogeneous group of poor prognosis patients with mRCC.

In our study, we have shown that the poor prognosis group is highly variable and the use of our SOSh scale results in the need to differentiate patients with mRCC. Current research suggests that cytoreductive surgery is indicated in patients with mRCC of favorable and intermediate prognosis according to IMDC. At present,

researchers have no clear consensus whether it is necessary to perform CN in patients with mRCC of poor prognosis in the conditions of modern systemic therapy. In our work, we tested in real clinical practice the provisions we put forward about the expansion of additional prognostic factors and the developed mathematical model SOSh on a group of patients with mRCC of poor prognosis.

In our modified SOSh model for personalized approach, we divided the heterogeneous group of poor prognosis into 2 subgroups: poor and very poor prognosis in mRCC patients and studied the effect of cytoreductive surgery on survival rates. The conducted study revealed statistically significant differences in OS in the subgroup of pooor prognosis in mRCC patients depending on the performance of CN (p=0.02), but not in the subgroup of very poor prognosis (p=0.28). The 3- and 5-year OS rates of performing CN in the SOSh poor and very poor prognosis subgroups were 34.0% and 9.8%, 20.3% and 7.2%, respectively. In our study, we found no difference in survival rates in mRCC patients with poor and very poor SOSh prognosis when metastasectomy was performed (p=0.114 and p=0.093). In our opinion, CN is indicated in patients of the subgroup of poor prognosis according to SOSh, and in the group of very poor prognosis the first stage of complex treatment should be drug systemic therapy.

The currently used IMDC model was developed for mRCC patients receiving targeted therapy. We studied the efficacy of first-line systemic therapy in patients with mRCC depending on prognosis in the modified SOSh model and comparison with IMDC prognosis groups. Our study showed that mRCC patients who received first- and second-line targeted therapy in IMDC and SOSh prognosis groups showed no difference in treatment response. We found that patients given immunotherapy and combinations in the first and second line received a difference in treatment response in patients with intermediate and poor prognosis according to SOSh mRCC.

At carrying out of systemic therapy of 1 line in patients with mRCC in groups of prognosis according to IMDC and modified SOSh scale the difference in responses in patients at application of immunotherapy of intermediate (p=0,032 and p=0,011) and poor prognosis according to SOSh (p=0,037 and p=0,0079) was noted. When 2nd

line systemic therapy was given to mRCC patients in the IMDC and modified SOSh prognosis groups, there was a difference in response in patients with poor prognosis according to SOSh with targeted therapy (p=0.014 and p=0.003); when using immunotherapy in the first and second line of intermediate (p=0.032 and p=0.011), (p=0.039 and p=0.017) and poor prognosis by SOSh (p=0.037 and p=0.0079), (p=0.042 and p=0.042).

Thus, in our opinion, there is a need not only to modernize the IMDC prognosis model, but also to separate the group of poor prognosis for a more effective approach to cytoreductive surgical interventions and personalized systemic therapy in patients with mRCC.

CONCLUSION

RCC has a poor prognosis at advanced stages with a 5-year survival rate of only 12% in case of metastatic disease [98]. At initial diagnosis, metastases of RCC are detected in 20-30% of patients, and in another 20-50% of patients they appear during the progression of the tumor process at various times after surgical treatment [9, 23, 113]. The presence of RCC metastases was an unfavorable prognostic factor for patients and influenced the course of the disease and significantly worsened the quality of life of patients. Survival rates of mRCC patients are disappointing; the median OS averaged from 4 to 20 months, and the expected 5-year OS <20% [123, 180].

In recent years, due to the clinical application of new immuno-oncologic drugs, progress has been made in the treatment of mRCC patients, but the results of treatment differ significantly from each other [182, 271]. In our opinion, these differences are related to the lack of comparisons of clinical and laboratory, pathomorphological characteristics of the tumor, the number of affected organs, the time of occurrence and localization of metastases. In addition, there are practically no works on the use of systemic drug therapy taking into account these factors and their influence on OS and PFS indices. Personalized models of patient survival rates based on the identification of prognostic factors for each patient have not been developed. To increase the survival rates when performing systemic therapy, in our opinion, it is necessary to take into account histological variants, the degree of tumor differentiation, the number of affected organs, the time of occurrence and localization of metastases, as well as laboratory data.

We retrospectively analyzed 981 patients with mRCC who received systemic therapy at the City Oncology Hospital No. 62 in Moscow and the City Oncology Dispensary in St. Petersburg from 2006 to 2022. We had all the necessary individual clinical and laboratory data, as well as information on the overall life expectancy with respect to this group of patients. All patients were dynamically monitored throughout

the treatment period. When analyzing the frequency of objective effects, time to progression, OS and factors affecting these parameters, we combined all 981 patients into a single group, since all patients received different variants of systemic therapy.

The impact of various clinical, morphologic, and laboratory factors on survival rates has been analyzed and either already included in prognostic models or considered as potential prognostic factors.

In our study, the rates of 3-year, 5-year OS in the total cohort of patients were 49.4±1.5% and 28.2±1.4% respectively. The median OS was 45.2 months, however, about 10% of mRCC patients die within the first year and another part of about 30% live for more than 5 years. Similar results were obtained in the work of S. Demasure et al. [179, 271]. In our work we also ask the question, what is the difference between the group of long-lived mRCC patients and patients who had a life expectancy of less than a year? And we also put a question what additional prognostic factors can influence the increase of survival rates in patients with mRCC?

When studying the influence of clinical, morphologic, and laboratory data on survival rates, we found that there were no statistically significant differences depending on age. According to the data of other studies [40, 49, 119], younger patients had advantages in the OS indices. Patients with a lower T, N index and women had better OS, which is consistent with our data and the results of previous studies [49, 68, 118, 194, 202, 210, 262].

Our study did not reveal statistically significant differences in OS and median OS according to gender and primary tumor localization ($p=0.055$ and $p=0.81$).

ECOG status had a statistically significant effect on OS in patients with mRCC ($p<0.0001$). With ECOG0 status, the 3-year and 5-year OS rates of patients were 82% and 73%, with ECOG1 – 69.3% and 44.8%, with ECOG2 – 45.8% and 18.8%, and with ECOG3 – 10.8% and 2.6%, respectively. In the work of D. Shin (2021), also ECOG – status influenced the rates of OS and PFS. In the work of K. Takahara (2020), low ECOG status, anemia and thrombocytosis were independent predictors of low ES.

Next, we studied the influence of tumor morphological characteristics on the survival rates of mRCC patients. According to the authors O. Abdel-Rahman (2017) and Haibin Wei (2021), high survival rates were observed in patients with chromophobe and clear cell cancer. Our data established statistically significant differences in OS rates depending on the histologic variant of cancer, with the luminal cell variant being the most favorable ($p<0.0001$). In our study, the incidence of light-cell cancer was 88.3%, papillary cancer – 4.7% and chromophobe cancer – 1.9%, which is consistent with the data of other authors [51, 59, 208]. The 3-year and 5-year OS rates were 53.3% and 31.3% for the luminal variant of the tumor; for non-small cell cancer – 27.1% and 10%, respectively. Similar to our work, previous studies have shown that patients with luminal cell carcinoma had a more favorable prognosis compared with patients with other histologic subtypes [141, 180]. Depending on the degree of tumor differentiation, 3-year and 5-year survival rates were 76.1% and 62.4%, 57.4% and 28.7%, 32.5% and 12.9% for highly, moderately and low-differentiated tumors, respectively. In our work, the degree of tumor differentiation significantly influenced survival rates, the best prognosis was in patients with highly differentiated tumors ($p<0.0001$). Our study is consistent with the works of many authors, although in Haibin Wei (2021), patients with moderately differentiated tumors had better OS than patients with highly differentiated tumors.

Laboratory parameters may also serve as prognostic factors for survival rates in mRCC patients.

In the present study, LDH and alkaline phosphate levels influenced the OS rates in mRCC patients ($p<0.0001$). When LDH was normal and elevated, the 3-year and 5-year OS rates were 53.0% and 31.32%, 42.5% and 22.3%, respectively. In current works, LDH is an important factor affecting survival rates in mRCC patients [128].

When alkaline phosphorus was normal and elevated, the 3-year and 5-year OS rates were 57.7% and 34.2%, 36.2% and 18.9%, respectively. Our data correlated with the data of previous studies [38, 61, 205, 240, 269].

We also performed a multivariate analysis of only significant laboratory parameters in mRCC patients. Only hemoglobin level was found to be the most important factor influencing the survival rate of mRCC patients ($p<0.0001$).

IMDC prognosis influenced the OS rates of mRCC patients ($p<0.0001$), as confirmed by Xiuqiong Chen (2021) and Hongzhe Shi (2022). The 3-year and 5-year OS rates of patients in the favorable prognosis group were 77.4% and 61.0%, 58.7% and 26.8% in the intermediate prognosis group, and 26.6% and 10.4% in the unfavorable prognosis group, respectively. In the study by Ko et al, S.M. Yip et al. unfavorable prognosis according to IMDC sharply reduced survival rates of mRCC patients [57, 259].

Thus, in addition to IMDC prognosis in mRCC patients, clinical, laboratory and pathomorphological parameters should also be studied in terms of personalized approach.

We also studied a group of mRCC patients of intermediate prognosis according to IMDC. This study revealed the heterogeneity of the intermediate prognosis group in terms of survival rates depending on the number of unfavorable factors, which is also confirmed in A. Sella (2017). Patients with 1 prognostic factor were more likely to have G1 tumors (13.2%/6.2%) and a more favorable ECOG status. Laboratory parameters showed no statistical differences between subgroups with 1 or 2 prognostic factors. Better survival rates were found in mRCC patients with 1 unfavorable prognostic factor ($p<0.0001$). Thus, the 3- and 5-year survival rates for subgroups with 1 and 2 unfavorable factors in mRCC patients were 68.9% and 38.5%; 43.6% and 12.9%, respectively. The duration of systemic therapy was statistically different, but no differences were found in the duration of its lines. The conducted study revealed a statistically significant increase in OS and median OS in patients with intermediate prognosis according to IMDC in the presence of non-visceral metastases ($p<0.0001$).

In single- and multivariate Cox proportional hazards model analyses, the degree of tumor differentiation, type and number of metastases, CN performance, and

presence of visceral metastases influenced OS rates in the presence of 1 adverse factor in mRCC patients of intermediate prognosis according to IMDC.

In single- and multivariate analysis of the Cox proportional hazards model of OS, also tumor differentiation, type and number of metastases, performance of CN, and presence of visceral metastases influenced OB rates in patients with 2 prognostic factors in the intermediate-risk population.

In a single-factor analysis of the Cox proportional hazards model, the degree of tumor differentiation and the number of metastases influenced the progression-free survival (PFS) rates in the presence of 1 unfavorable factor in patients with mRCC of intermediate prognosis according to IMDC. In multivariate analysis, in addition to the previous factors, the type of metastases also influenced survival rates.

In a single-factor analysis of the Cox proportional hazards model, the type of metastases, their number, and the number of affected organs in the presence of 2 unfavorable risk factors in patients with intermediate prognosis according to IMDC mRCC influenced PFS rates. In multivariate analysis, the type and number of metastases had an impact.

We searched for the influence of the most important prognostic factors in patients with favorable and poor prognosis of mRCC based on the Cox proportional hazards model.

In single-factor analysis, metastasis type, metastasectomy performance, presence of visceral metastases, and presence of bone metastases influenced OB rates in mRCC patients with favorable prognosis according to IMDC; in multivariate analysis, gender, presence of visceral metastases, and alkaline phosphatase level were additional influential prognostic factors.

In a single-factor analysis, the degree of differentiation, type and number of metastases, CN and metastasectomy, visceral metastases, liver and lymph node metastases, and alkaline phosphate, LDH, and sedimentation levels influenced RR in IMDC-positive mRCC patients. In multivariate analysis, the degree of differentiation, the type and number of metastases, the performance of HE and metastasectomy, and the presence of visceral metastases were influential.

In a single-factor analysis, metastasis type, number of metastases, number of affected organs, presence of bone metastases, and alkaline phosphate levels influenced PFS rates in patients with favorable prognosis according to IMDC mRCC. In multivariate analysis, the type of metastases and the presence of brain metastases were influential.

In a single-factor analysis, the degree of differentiation, number of metastases, number of organs with metastases, presence of liver and lymph node metastases, and levels of alkaline phosphate, LDH, and ESR influenced PFS rates in IMDC-positive mRCC patients. Multivariate analysis showed the influence of differentiation degree, number of metastases and lymph node involvement as factors affecting the PFS in IMDC patients with mRCC.

Thus, based on our study, we have identified various prognostic factors affecting the OS and PFS in mRCC patients with favorable, intermediate, or unfavorable prognosis according to the IMDC scale.

In all groups, factors related to the characteristics of the metastatic disease itself were influential. At the same time, as the prognosis worsened, clinical and laboratory factors were included, which became significant predictors reflecting the increasing organ dysfunction.

Next, in our study, we examined the RFP (RFP) groups and evaluated prognostic factors affecting survival rates in 578 mRCC patients.

Depending on the time of appearance of distant metastases after radical treatment, patients were divided into 4 groups:

- Group 1 – less than 1 year – 174 patients (30.1%);
- Group 2 – from 1 to 3 years – 176 (30.4%);
- Group 3 – 3-5 years – 67 (11.6%);
- Group 4 – more than 5 years – 161 (27.9%).

In these subgroups, the rates of 3- and 5-year OS of mRCC patients were 46.2% and 27.8%, 59.5% and 32.9%, 57.6% and 44.4%, 66.8% and 42.1%, respectively. Thus, we observed better OS rates in patients with a RFP of more than 3 years in subgroup 3 and 4 ($p=0.012$). We also looked in multivariate analysis the

factors influencing the duration of RFP in mRCC patients in the total cohort of patients and separately in each of the 4 subgroups.

In multivariate analysis, only the degree of tumor differentiation ($p<0.0001$) had a statistically significant effect in all RFP in mRCC patients. When evaluating the influence of prognostic factors in each of the 4 groups of mRCC in our study, we obtained the following results. Thus, in the groups of up to 1 year, 1 to 3 years, and the group with more than 5 years of RFP, the degree of tumor differentiation according to Fuhrman had a statistically significant effect on survival rates. In the study of the 3 groups with 3 to 5 years of RFP, none of the factors had a statistically significant effect on survival rates.

Thus, in Chapter 3, we analyzed the impact of various constitutional, clinical-morphologic, and laboratory factors on survival rates in mRCC patients, which are either already included in prognostic models or considered as potential prognostic factors.

The analysis of the results of our study showed that the survival rates of mRCC patients were influenced by the number of affected organs and the time of their occurrence, localization of metastases, pathomorphological characteristics of the tumor and clinical and laboratory parameters. Our study revealed that the OS indices were worse with increasing number of affected organs ($p=0.0008$), as confirmed in the work of S. Dudani (2021). In the work of C. Karacin et al. 87.6% of mRCC patients had ≥2 sites of metastasis. In our study, the 3-year and 5-year OS rates were 62.4% and 36.1% for 1 organ lesion in mRCC patients, 56.1% and 27.0% for two organs, 41.3% and 29.3% for three organs, and 58.8% and 31.1% for four or more organs, respectively. According to D. Santini et al., metastases in one organ are rare in mRCC, and our study showed that the majority of patients had 1 organ affected.

Localization of metastases and their number were important in the prognosis of patients with mRCC. There are a limited number of reports in the literature on the influence of the number and localization of metastatic foci in patients with mRCC on survival rates. In the study of A. Pecoraro (2020), it was reported that the lungs were the most frequent metastatic site in patients with mRCC. In the work of other

investigators, metastases to bone, lymph nodes, and liver were frequent along with lung metastases, having a negative impact on overall survival rates. Metastases to the liver had the worst prognosis in mRCC patients among these localizations [49, 210, 257]. In our work, we noted that metastases were most often detected in the lungs (66.7%), bones (38.4%), lymph nodes (34%), liver (14.4%), and adrenal gland (14.4%), which is consistent with the data of other authors [28, 239, 263]. Brain lesions in our study were statistically significantly more frequent in patients with intermediate prognosis mRCC with 1 unfavorable sign.

Our study showed that combinations of affected organs are of great importance with regard to therapy and survival rates. The most frequent combinations in multi-organ metastases were: lung + lymph nodes (9.2%) bone + lung (6.4%), bone + lung + lymph nodes (3.5%). In Haibin Wei (2021), the highest frequency of metastasis combinations was observed in patients with bone and lung metastases – 10.82%.

We noted statistical differences depending on the organ in which the isolated metastatic lesion was observed. We noted lower rates of OS in isolated metastases in lungs, bones and lymph nodes in mRCC patients. In patients with isolated lung metastatic lesions (N=191), 3-year and 5-year OS rates were 44.5±% and 27.6%, respectively. For patients with isolated bone lesions (N=89), the 3-year and 5-year OS rates were 37.4% and 11.9%, respectively. For patients with isolated metastatic lymph node involvement (N=34), the 3-year and 5-year OS rates were 38.9% and 21.4%, respectively. The median OS was 34.4, 27.9 and 26.8 months, respectively.

In the conducted study the survival rates of mRCC patients depending on the prevalence of metastases and clinical and morphologic parameters were studied. Based on the modern classification, solitary, single and multiple metastases in mRCC patients were identified and distributed as follows: 90 (9.2%), 252 (25.7%) and 639 (65.1%) patients, respectively. In contrast to the study by Haibin Wei (2021), where 50.6% of mRCC patients showed solitary metastases and 49.4% showed single and multiple metastases. We found that an increase in the number of metastatic foci is significantly associated with unfavorable prognosis and poor survival rates, which is supported by the works of Q. Guo (2018), Z. Lu (2022). In our work, the 3-year

and 5-year OS rates of patients with solitary, single and multiple metastases of RCC were 80.7% and 56.1%, 72.5% and 38.3%, 33.5% and 13.8%, respectively. Our studies demonstrated that the survival rates of mRCC patients were influenced not only by the number of metastases, but also by clinical and laboratory parameters, which should be used to develop diagnostic criteria.

Patients with multiple metastases of RCC had a lower degree of differentiation in 55.0%, and patients with solitary metastases on the contrary had light-cell carcinomas of high differentiation in 38.9% of cases, respectively. The age of the patients did not differ significantly between the groups, nor did the serum total calcium and neutrophil counts. Hemoglobin levels were significantly lower in patients with multiple metastases. At the same time, the levels of alkaline phosphate, LDH, ESR and peripheral blood platelet count were higher in patients with multiple metastases. Interestingly, platelet count and LDH were lower in patients with single RCC metastases compared with solitary metastases. Patients with solitary metastases were more likely to have no lymphogenic metastases. Patients with multiple RCC metastases were more likely to have low-differentiated tumors.

The peculiarities of metastatic lesions were noted in patients with solitary metastases. Highly differentiated tumors were detected more often in these patients. All patients (100%) with metastases to the lungs, bones and brain had metastases of clear cell RCC, and papillary cancer was more often detected in liver lesions in 16.7%. In Shaan Dudani (2021), patients with clear cell RCC were almost twice as likely to metastasize to the lungs as patients with chromophobe RCC, and vice versa when liver metastases were present. In patients with solitary metastases of RCC, lymphogenic metastases were extremely rare at 2.2%, more frequent in the light-cell variant G3 (6.7%) and in the papillary variant G2 (33.3%). Metastases to the brain were not detected in G1, and in G2 and G3 – in 9.3% and 26.7%, respectively. According to literature data, brain metastases to the brain were detected in 8% of mRCC patients with the luminal cell variant of tumor and a lower incidence of metastasis in papillary (2%) and chromophobe (3%) variants of RCC [88, 100, 150, 190]. In comparison with the cited literature sources, in our work we studied

solitary metastases to the brain, lymph nodes in mRCC patients not only by morphologic subtypes, but also by the degree of malignancy. Depending on the histological variant and tumor differentiation degree statistically significant differences (p=0.01) were revealed only for lymph node lesions. For other localizations of metastases in patients with solitary metastases of RCC statistically significant differences were not revealed (p>0.05). In Cox single-factor analysis the degree of tumor differentiation according to Fuhrman, metastases to the brain and metastasectomy were the factors influencing the OB indices in patients with solitary metastases of RCC. In multivariate analysis according to Cox, the degree of tumor differentiation according to Fuhrman, brain metastases were the factors influencing the survival rates in patients with solitary metastases of RCC. Thus, the study of survival rates in patients with solitary metastases of RCC in multivariate analysis showed the influence of the degree of tumor differentiation according to Fuhrman, as well as the presence of brain metastases.

In mRCC patients with single metastases, the G1 and G2 light-cell tumor variant was predominant (68.2%), but the non-small-cell variant was more common (7.1%). Liver involvement was rarely observed (2%), but lymph nodes were more frequently involved (11.1%). Lung and bone remained the dominant localization of metastases (55.9% and 32.9%, respectively). In patients with single metastases of mRCC, isolated lung and bone lesions were noted at G1-G3, 45.3; 32.9; 43.3% and 12.8; 29.5; 21.7%, respectively. The third place in terms of occurrence was the combined lesion of these localizations at G1 (6.9%), and at G2 – metastases to the adrenal gland (7.9%). In patients with single metastases of non-small cell RCC depending on the histologic variant and differentiation degree, differences (p=0.04) were revealed for metastatic lesions of the adrenal glands and liver. For other localizations of metastases in patients with single metastases of RCC no statistical differences were revealed. In chromophobe and papillary cancer the adrenal glands were never affected, and in clear cell cancer rarely (slightly more often in G1 tumors). In papillary RCC, metastases to the liver were found in 1/3 of patients. In single-factor analysis according to Cox, the degree of tumor differentiation according

to Fuhrman, metastases to bones and lungs, elevation of ESR and alkaline phosphatase, as well as metastasectomy were the factors influencing the AE values in patients with single metastases of RCC. In Cox multivariate analysis, the type of metastases, brain metastases, LDH elevation, and metastasectomy were the factors influencing the survival rates in patients with single metastases of RCC. Thus, the study of survival rates in patients with single metastases of RCC in multivariate analysis showed the influence of the type of metastases, LDH level, and the presence of brain metastases.

In patients with multiple metastases, G2-G3 variants of clear cell cancer predominated (88.9%). There were also other histologic variants, more often low-differentiated (13.1%). In patients with non-small cell RCC the localization of metastatic lesions in lungs was 77-86%, bones – 50%, lymph nodes – 50-55%, liver – 26-33% and kidneys – 7.3-11.5%. In patients with non-small cell cancer, lung lesions were 50-70%, liver 40%, bone 25-33%, lymph nodes 33% and kidney 20-28%. In our work we noted an increase in liver and kidney lesions in non-small cell variant of RCC. Adrenal lesions were rare, but a high percentage of lesions in G2 non-small cell carcinoma (19.2%) and papillary carcinoma (17.6%) was noteworthy. In Cox single-factor analysis, tumor histological variant, Fuhrman tumor differentiation degree, type of metastases, metastases to bone, lung, liver; elevation of alkaline phosphatase, LDH and ESR, as well as performance of CN, metastasectomy and radiotherapy were the factors influencing the rates of OS in patients with multiple metastases of RCC. At multivariate analysis according to Cox, tumor histological variant, tumor differentiation degree according to Fuhrman, type of metastases, metastases to the brain, as well as performance of CN, metastasectomy were the factors influencing the survival rates in patients with multiple metastases of RCC. Thus, the study of survival rates in patients with multiple metastases of RCC in multivariate analysis showed the influence of tumor histological variant, tumor differentiation degree according to Fuhrman and type of metastases, performance of CN and metastasectomy, as well as the presence of brain metastases**.**

We studied the dependence of survival rates in patients with synchronous and metachronous metastases of RCC. The lesion of 1 and 2 organs was more often observed in patients with metachronous metastases (53.8%), and in synchronous metastases multiorgan lesion was established (67.9%). In the work of F. Donskov et al. synchronous metastases were found in about 15% of patients with mRCC. According to T. Chandrasekar (2017), synchronous metastases to the lungs are the most common in patients, followed by metastases to bone, liver and brain. This is also supported by the data of our study. OS rates differ between patients with synchronous and metachronous metastases of RCC. This is also confirmed by the works of S.H. Kim (2017) and S. Han Kim (2017). In patients with metachronous and synchronous metastases, the 3-year and 5-year OS rates were 53.7% and 35.1%, 38.2% and 18.5%, respectively ($p<0.0001$). Importantly, survival rates are much worse in the presence of 2 risk factors and in patients with synchronous metastases. In the work of M. Callea et al. (2016), noted that understanding the prognostic differences between synchronous and metachronous metastases of RCC is important for the development of treatment strategies for mRCC in the era of systemic therapy. Patients with synchronous RCC metastases had a poor prognosis according to IMDC and ECOG status, a low degree of differentiation, the presence of lymphogenic metastases, and a greater number of organs affected by metastases. Anemia and elevated ESR were more frequently observed in patients with synchronous metastases, and normal platelet counts and alkaline phosphatase were observed in patients with metachronous metastases of RCC.

Thus, the results of our study showed that despite the existing tendency of prevalence of metastases to lungs, bones and lymph nodes of RCC, histological variants, the degree of tumor differentiation and laboratory data impose an imprint on the peculiarities of the metastatic process, which should be taken into account in the approach to the prescription of systemic therapy.

We further evaluated prognostic factors and their impact on CN efficacy in 330 mRCC patients.

The influence of prognostic factors on the OS of patients undergoing CEA was evaluated. The cumulative 3- and 5-year survival rates in patients with and without CN were 48.2% and 11.3%, 20.5% and 8.2%, respectively. Performing CN in the overall cohort of patients statistically significantly increased survival rates ($p<0.0001$). Differences in IMDC prognostic group survival rates were found both with and without CN performance. The 3- and 5-year OS rates of patients with CN in favorable, intermediate, and unfavorable IMDC prognostic groups were 95.7% and 80.1%, 75.9% and 29.2%, 29.5% and 12.1%, respectively, and in the absence of CN the groups were 50.0% and 50.0%, 27.5% and 27.5%, 6.3% and 0%, respectively. In single-factor analysis in patients who underwent CN the histological variant and tumor differentiation degree according to Fuhrman, the number of metastases, ECOG status, the presence of liver metastases, as well as hemoglobin, alkaline phosphatase and LDH levels were the factors influencing the RR in patients with mRCC at CN. In multivariate analysis, age (45-59 and 60-74 years old), Fuhrman tumor differentiation degree, number of metastases, ECOG status, bone metastases and hemoglobin level were additional factors influencing the OS in mRCC patients.

We have studied the influence of combined palliative surgical treatment in the volume of CN and metastasectomy in 62 patients with mRCC on survival rates, and we have considered clinical, laboratory, pathomorphologic factors influencing survival rates. In this cytoreductive intervention, the 3- and 5-year OS rates of patients when performing CN in combination with and without metastasectomy were 47.2% and 27.1%, 38.9% and 17.6%, respectively. In the groups of favorable, intermediate and unfavorable prognosis according to IMDC the rates of 3- and 5-year OS of patients were 100% and 100%, 64.7% and 23.5%, 38.4% and 23.1% respectively ($p=0.004$). Meanwhile, the median OS was 99.8, 42.9 and 25.1 months, respectively. In single-factor analysis, ECOG status, number of metastases, and hemoglobin level were factors influencing the OS rates in mRCC patients. In multivariate analysis, age (older than 75 years), histologic type, ECOG status, number of metastases, and bone metastases were additional prognostic factors

affecting OS in mRCC patients who underwent cytoreductive nephrectomy and metastasectomy.

In our study, we also investigated prognostic factors in 73 mRCC patients who did not undergo CN. Cytoreductive surgery was not performed mainly because of low ECOG status due to visceral crisis, and the 3- and 5-year OS of patients in the overall cohort without CN were 20.5% and 8.2%, respectively. At the same time, the median OS was 11 months. In the IMDC favorable, intermediate, and poor prognosis groups, the 3- and 5-year OS rates of patients in the absence of CN were 29.0% and 29.0%, 6.0% and 0%, respectively. The median OS was 22.9 and 9 months, respectively. The study revealed statistically significant differences in OS and median OS depending on IMDC prognosis in patients with mRCC in the absence of CN ($p=0.0024$). In single-factor analysis, the degree of tumor differentiation according to Fuhrman, ECOG status and presence of brain metastases, hemoglobin and platelet levels were the factors influencing the RR. In multivariate ECOG status and brain metastases were additional factors influencing the OS in patients who did not undergo CN.

The study of the influence of prognostic factors on OS in 226 patients with mRCC who underwent metastasectomy was carried out. The 3- and 5-year OS of patients undergoing metastasectomy was 60.0% and 43%, respectively. The median OS was 49 months. We have studied the influence of metastasectomy on survival rates in mRCC patients of different prognostic groups according to IMDC. When metastasectomy was performed in the IMDC prognostic groups, the 3- and 5-year survival rates were 83.9% and 75.7%, 57.8% and 28.1%, 36.0% and 21.3%, respectively. The median OS also differed and was 84.5, 41.8, and 20.9 months, respectively. The conducted study revealed statistically significant differences in OS and median OS depending on IMDC prognosis in mRCC patients undergoing metastasectomy ($p<0.0001$).

In patients with poor prognosis with and without metastasectomy, the 3- and 5-year OS rates were 36.8% and 20.9%, 24.3% and 9.2%, respectively; in patients with intermediate prognosis, 60.5% and 28.2%, 57.7% and 25.3%, respectively; and in

patients with favorable prognosis, 81.7% and 71.4%, 73.8% and 51.4%, respectively. Thus, in our study, in the groups of poor and favorable prognosis, we obtained differences in OS rates in mRCC patients, and in the group of intermediate prognosis when metastasectomy was performed, no differences in OB rates were found. In single-factor analysis, the degree of tumor differentiation, number and type of metastases, ECOG status, presence of bone metastases, as well as hemoglobin, alkaline phosphatase and ESR levels, performing CN, performing complete metastasectomy and performing metastasectomy before systemic therapy were the factors influencing the OS in mRCC patients who underwent metastasectomy. In multivariate analysis, ECOG status, tumor differentiation degree, CN and radiation therapy, complete metastasectomy and metastasectomy prior to systemic therapy were the factors influencing OS in mRCC patients.

In our study, we found that in a single-factor analysis, the greatest number of additional factors that should be taken into account when choosing cytoreductive interventions was found in patients with mRCC before performing CN and metastasectomy. It was also noted that most prognostic factors were similar in CN (+) and (-), except for alkaline phosphate, LDH; bone, liver and brain metastases. The multivariate analysis revealed that the greatest number of additional factors that should be paid attention to when choosing cytoreductive interventions was found in patients before CN and combination of CN and metastasectomy. At the same time, all additional prognostic factors influencing the survival rates of mRCC patients are practically similar in these cytoreductive surgeries.

In our work we have shown that not all patients with mRCC are indicated for cytoreductive surgery. The main factors that had a statistically significant impact on the survival rates of mRCC patients were the degree of tumor differentiation according to Fuhrman, the number of metastases, as well as metastases to the liver and brain. Thus, the IMDC model is currently insufficient to select mRCC patients for cytoreductive surgery. Based on our study, we believe that additional prognostic factors that influence the choice of cytoreductive interventions in patients with mRCC, in addition to the IMDC prognosis, are the degree of tumor differentiation,

type and number of metastases, as well as the presence of bone, lung and brain metastases.

Since the beginning of the 21st century, tremendous progress has been made in the treatment of mRCC. Understanding the molecular profile of tumor cells has led to the development of systemic therapies, and the study of antitumor immunity has changed the clinical presentation of the disease [39, 219, 240]. The paradigm has changed twice in the last decade, improving the outcomes of mRCC patients through the use of combination regimens with ICI and TKI (axitinib plus pembrolizumab or avelumab) [256, 274].

Such drug combinations are now approved and are part of the ever-expanding armamentarium for the treatment of mRCC patients. Nevertheless, this has necessitated the discovery of predictors and prognostic biomarkers that can personalize the treatment of mRCC patients in order to improve the efficacy and reduce the toxicity of therapy.

We analyzed the outcome of therapy by lines in patients with mRCC depending on the type of systemic therapy and histological characteristics of the tumor. 981 mRCC patients received systemic therapy, 667 (68.0%) of them received 2 lines, 348 (35.5%) – three lines of systemic therapy. The number of patients in line 4 was 138 (14.1%), 49 (5%) in line 5, and 23 (2.3%) patients in line 6.

In the first line, 773 (78.8%) patients received TKI, 169 (17.2%) received cytokine therapy, 34 (3.5%) patients received ICI therapy, and 5 (0.5%) patients received chemotherapy.

The overall response to treatment in the 1st line of systemic therapy in mRCC patients was 9.5%. Complete response was registered in only 1% of patients, partial response in 8.5%, stabilization in 42.4% and progression in 39.8% of patients. Our data are consistent with the works [30, 107, 179, 227].

In the first line of therapy, depending on the type of systemic therapy and histological characteristics of the tumor, an analysis was performed in groups of patients with single, solitary, and multiple metastases, and the number of affected organs at the time of therapy initiation was taken into account. In subsequent lines

of therapy the prevalence of metastases and the number of affected organs were excluded due to the progression of tumor process and loss of relevance of such subdivision by the nature of metastatic process. Therapy outcomes were conditionally divided into favorable, including all cases of complete response, partial response and stabilization, and poor – progression on the background of treatment, death or deregistration.

The frequency of outcomes in the 1st line differed significantly: complete response (3.3%) and deregistration (3.1%) was observed more often in patients with solitary metastases of RCC, stabilization occurred in case of single metastases (51.1%), partial response (9.4%) and lethal outcome (6.2%) – in case of multiple metastases. In patients with multiple metastases of RCC treated with immunotherapy, a partial response was observed in 45.1%. Stabilization and progression were observed almost equally (22.6% and 25.8%, respectively). In patients with multiple metastases of RCC, statistically significant differences in the incidence of conditionally favorable and unfavorable outcomes were found depending on the number of affected organs and the drug administered ($p=0.000176$). In patients with solitary and single metastases such dependence was not observed due to frequent involvement of one organ. In patients with solitary metastases of RCC, changes of 2 or 3 organs were rare. Irrespective of the number of affected organs, the frequency of favorable outcome with ICI was higher than with other treatment options, reaching 60% on average, slightly higher in case of a single organ lesion 66.7%.

The frequency of favorable and poor outcomes significantly differed depending on the histological type of mRCC and drugs in patients with multiple metastases, and had no differences in solitary and single metastases. Administration of ICI in the 1st line resulted in a favorable outcome in 72.73% of patients with clear cell cancer and in the only patient with non-small cell cancer.

ICI in 1 patient with solitary metastases and 2 patients with single metastases resulted in a favorable outcome. In 11 patients with multiple metastases a favorable outcome was observed in 72.7% of cases. ICI was used with a favorable outcome in only one patient with multiple metastases.

Comparison of the frequency of outcomes depending on the degree of tumor differentiation and the group of drugs used revealed that the frequency of favorable and poor outcomes differed in multiple metastases of RCC and had no differences in solitary and single metastases. Immunotherapy with checkpoint inhibitors ended with favorable outcome in all patients with G1, in G2 and G3 in 50% and 70% of patients, respectively. TKI demonstrated efficacy in 70.6% of patients with solitary and multiple metastases of RCC.

The 2nd line systemic therapy was performed in 667 (68%) patients with mRCC. Overall response was achieved in 43 patients (6.4%); complete response was recorded in 4 (0.6%) patients, partial response in 39 (5.8%), stabilization in 330 (49.4%), progression in 243 (36.4%), withdrawal in 22 (3.2%) and death in 29 (4.3%) patients. Similar results were reported by M.G. Vitale (2016), T. Buchler (2017), R. Lakomy (2017), A.Y. Shah (2019), V. Mollica (2021), R. Iacovelli (2022).

It should be noted that when using systemic therapy of the 2nd line, stabilization of the disease was recorded more often than in the 1st line (49.4%/42.4%). In the 2nd line immunotherapy showed maximum efficacy with achievement of stabilization in 64.86% of mRCC patients. Favorable outcome was recorded at its administration in 100% of cases at G1 and 80% and more at G2 and G3. Immunotherapeutic drugs demonstrated the best efficacy in light-cell and non-small-cell variants of mRCC (89.5% and 75%, respectively).

Third-line systemic therapy was given to 348 (35.5%) mRCC patients. Complete response was recorded in 1 (0.3%) patients, partial response in 17 (4.9%), stabilization in 188 (54.0%), progression in 116 (33.3%), withdrawal in 9 (2.6%) and death in 17 (4.9%) patients. Our data are in agreement with the works of H. Ishihara (2018), N. Takahito (2018), T. Fujita (2019), S. Naito (2019).

It should be noted that the percentage of mRCC patients with disease stabilization (54.0%) on line 3 therapy increased compared to previous lines of therapy.

Analysis of the frequency of outcomes in 3 lines did not reveal statistically significant differences depending on the treatment ($p=0.097750$). When dividing

outcomes into conditionally favorable and conditionally unfavorable, no statistically significant differences were obtained depending on the therapy performed in mRCC patients (p=0.893322).

ICI was effective in 80% of patients. The efficacy of ICI in light cell variant of RCC was 90%. ICI gave a favorable outcome in G1 tumors in 100% of cases, and as the differentiation decreased (59-56%) its efficacy decreased, but it was still the best in comparison with other groups of drugs.

The 4th line systemic therapy was performed in 138 (14.1%) patients, the 5th line – in 49 (5%) patients, the 6th line systemic therapy was performed in 23 (2.3%) patients with mRCC. On the 4th-6th lines of systemic therapy in mRCC patients the most frequent progression of the process was observed, somewhat less frequently – stabilization. Partial response was the most favorable outcome and was observed in only 6.3% of cases, almost as often patient death was registered (5.3%). Similar results were obtained in the works of B. Ralla (2017), N. Takahito (2018), I. Stukalin (2018), S. Naito (2019), S. Shira (2022).

TKI therapy allowed achieving a favorable outcome in 73.33% of mRCC patients. Partial response was extremely rare with TKI (4.35%), and disease progression was observed almost as often as stabilization. Administration of chemotherapy and cytokines always resulted in an unfavorable outcome. No significant differences in the frequency of outcomes depending on the histologic variant of RCC with different treatments on follow-up lines were found. TKI with checkpoint inhibitors was effective in all patients with a clear cell variant of the tumor. When TKI was administered, a favorable outcome was observed in the light-cell and non-small-cell variants of RCC in 49.07% and 33.33% of patients. In our study, the efficacy of all groups of drugs continued to decrease in the 4th-6th lines of therapy. However, TKI demonstrated the highest efficacy, which gradually decreased as the degree of tumor differentiation decreased. TKI demonstrated a sharply decreasing to 38.89% rate of favorable outcome for G2 tumors, which was slightly higher for G3 tumors.

We have found that the best results in the application of systemic therapy in mRCC patients in all lines were obtained with the use of immuno-oncologic drugs and TKI. Regardless of the number of affected organs, number of metastases and tumor differentiation degree, the frequency of favorable outcome was higher with immunotherapy than with other treatment options in mRCC patients.

Currently, significant progress has been made in systemic therapy of mRCC, which allows to significantly prolong the survival rates of such patients. Our studies have shown that when a new line of therapy is administered to patients, there is a decrease in the rate of complete and partial response, but also a decrease in the rate of disease progression; however, this trend was observed until the 4th line of therapy. In subsequent lines of systemic therapy, mRCC patients with a complete response are completely absent, with an increasing incidence of partial response in lines 4 and 5. The percentage of mRCC patients with disease stabilization increases, while the number of patients and duration of therapy decreases.

Our study showed that the best results were obtained when ICI and TKI were administered. IRCC patients who received ICI showed better survival in all lines of systemic therapy. In our work, we noted that it is also necessary to take into account the combinations of drugs that the patient received in different lines of therapy.

We analyzed the effect on the survival rates of mRCC patients of different variants of combinations of systemic drugs without taking into account cytokine therapy and chemotherapy, which was performed in the pre-targeting era. Systemic drug therapy in lines 1-3 was performed by the following groups of drugs: TKI, ICI (PD-1, PD-L1), and m-TOR inhibitors. One line of systemic therapy was performed in 376 mRCC patients, of which TKI therapy was performed in 356 (94.7%) patients, 11 (2.9%) patients received ICI, therapy with m-TOR inhibitors was performed in 9 (2.4%) patients. In the comparative analysis of clinical and morphological characteristics of mRCC patients, m-TOR inhibitors were more often prescribed to patients with non-small cell variants of mRCC, while ICI and m-TOR inhibitors were less often prescribed in tumors of high differentiation degree. There were no differences in the other characteristics compared. For mRCC patients who received

a single line of systemic therapy, the 3-year, 5-year, and 10-year OS rates were 30.3%, 14.7%, and 4.2%, respectively. In patients who received TKI therapy, the 3-year and 5-year OS rates were 25.7% and 17.8%; for the ICI group, the 1- and 3-year OS rates were 61.2%; and for the m-TOR inhibitor group, the 3- and 5-year OS rates were 21.2%, respectively. Thus, there were no statistical differences in survival rates in mRCC patients who received 1 line of systemic therapy depending on the systemic drug (p=0.27).

Systemic therapy in 2 lines was performed in 272 patients with mRCC, who were categorized into 4 groups depending on different combinations of systemic drugs: TKI + TKI – 211 (77.3%) patients;

- TKI + ICI and – ITC + TKI – 17 (6.2%) patients, of which 15 (5.5%) patients received ITC in the first line, immunotherapy in the first line was given to 2 (0.7%) patients;
- TKI + m-TOR inhibitor – 32 (11.7%) patients;
- m-TOR inhibitor + TKI – 12 (4.4%) patients.

The 3-year, 5-year, and 10-year OS of all patients who received two lines of systemic therapy were 43.7%, 29.8%, and 7.6%, respectively. In patients who received two lines of therapy the indices of 3-year, 5-year and 10-year OS of the patients were 50.2%, 29.5% and 5.4±% for the first subgroup, respectively; for the second subgroup – 76.9%; for the third subgroup – 56.2%, 40.6% and 6.2%; for the fourth subgroup – 28.2%, 18.8% and 0%, respectively. The OS rates differed between subgroups (p=0.007), with the combination of ITC + PD-1 being the most effective. Thus, our study showed that it was the combination of systemic drugs that had an impact on the rates of OS in patients with mRCC. We found that the best results of survival rates were demonstrated by the combination of TKI+ICI, the worst – by m-TOR inhibitor+TKI. In the work of Viola J. Chen, 2019 found no direct evidence of universal cross-resistance among several systemic therapy options for mRCC.

Third-line systemic therapy was given to 149 mRCC patients, who were categorized into 3 groups depending on different drug combinations:

- TKI+TKI+TKI – 78 (45.1%) patients;
- TKI + TKI + m-TOR inhibitor – 46 (26.6%) patients;
- TKI + m-TOR inhibitor + TKI – 25 (14.5%) patients.

For mRCC patients who received three lines of systemic therapy, the 3-year, 5-year, and 10-year OS rates were 59.2%, 38.8%, and 8.9%, respectively. In patients who received three lines of therapy, the 3-year, 5-year, and 10-year OS rates were 54.7%, 39.7%, and 8.6% for the first subgroup; 44.6%, 35.6%, and 4.6% for the second subgroup; and 60.0%, 32.1%, and 9.2% for the third subgroup, respectively. Differences in OS rates depending on the combination of systemic drugs in mRCC patients were not statistically significant ($p=0.85$).

The combination of drugs in three lines of systemic therapy in patients with mRCC had no effect on survival rates. At the same time, our study showed that the best survival rates in the 1st-3rd lines of systemic therapy were in patients with mRCC who received the combination of TKI+ICI (or ICI+TKI).

Radiation therapy and administration of intermittent systemic therapy in mRCC patients increased the rates of OS, as confirmed in the works of Y. Zhao (2017) and M. Prunty (2021). In the study of Giulio Francolini (2022), stereotactic radiotherapy in combination with ICI improved OS, PFS, and showed a higher degree of local control of metastatic lesions.

Mathematical survival prediction models are increasingly being applied in oncourology for personalized treatment approaches. This is particularly important nowadays, as there is an urgent need for reliable prognostic biomarkers in mRCC. These advanced prognostic models can be used to identify mRCC patients with favorable and unfavorable prognosis who are more suitable for systemic therapy or surveillance.

Based on the clinical, laboratory, and pathomorphologic study of mRCC patients, we created a logistic regression model for predicting the 5-year OS of mRCC patients and evaluated it using ROC analysis. The obtained logistic regression model for predicting the 5-year OS using the 4 most significant predictor factors was statistically significant ($p<0.001$) and 93.3% classifiable. The sensitivity of the model

was found to be 98.3% and specificity was 62.3%. This model allows us to evaluate the role of each predictor in producing a predictive value for the probability of 5-year survival. ROC analysis confirmed the excellent quality of the model – the area under the curve was 93.9% (95DI – 91.4÷96.5%), sensitivity 89.3% and specificity 80.5% with a cut-off point equal to 80.6%.

The next step was to calculate a multifactor model for predicting survival time based on the most significant predictors. We plotted the survival time of mRCC patients at the average values of the factors included in the model, at their worst combination, the most favorable combination, and by the factors identified in a particular patient. The 10-year OS of mRCC is on average about 5% of operated patients. The median OS is in the range from 4.5 to 5 years. The lower quartile is close to 3 years, and the upper quartile is about 6.5 years. With a favorable combination of prognostic factors, 10-year OS rates reach more than 60%, with the median OS out of reach and the upper quartile around 9 years. With an unfavorable combination of prognostic factors, OS rates are less than 4 years. The upper quartile is just over 6 months, the median OS is just over a year, and the lower quartile is between 1.5 and 2 years.

Thus, the logistic regression model for predicting 5-year survival in patients with mRCC was statistically significant ($p<0.001$) and sufficiently classifiable (93.3%). In addition, it allows us to evaluate the role of each predictor in the development of the prognostic value of the probability of 5-year survival in mRCC patients.

Thus, based on the 10 most significant factors ($p<0.001$), a model for assessing the 10-year OS of mRCC patients was obtained.

Further, in our study, based on the established prognostic factors, we performed the creation of a modified model in mRCC patients that can be used for practical healthcare.

In the current era of immuno-oncology drugs and their combinations, the prognosis of patients with mRCC is determined by the IMDC model alone. However, we know that renal tumor is a heterogeneous disease. As we described previously the

overall cohort of 981 mRCC patients, they were divided into 3 prognosis groups in our study. Thus, the number of favorable prognosis patients was 226 (23.0%), intermediate and poor prognosis 352 (35.9%) and 403 (41.1%) patients, respectively. But at present, according to the results of our work and the works of other authors [25, 57, 82, 83, 104, 136, 173], it has been found that the IMDC scale does not reflect a personalized approach to prognosis in patients with mRCC. This model does not include such factors, which not only from our point of view, but also according to other authors [25, 104, 136], are important from the point of view of prognosis in mRCC patients. These are the degree of tumor differentiation according to Fuhrman, the type and number of metastases, the performance of CN and metastasectomy, the presence or absence of visceral metastases. In this regard, we believe that the revision of the established IMDC prognostic model is highly relevant today and it is necessary to try to supplement or replace some prognostic factors with more significant ones in patients with mRCC on a large clinical material.

In this study, we performed Cox multivariate analysis to identify statistically significant prognostic factors affecting survival rates in 981 mRCC patients. Using the Kaplan-Meier method, we analyzed the median OS of patients according to each prognostic factor in the 3 prognostic groups. As a result, we identified and examined 8 significant prognostic factors out of 15 prognostic factors in 981 mRCC patients, including type and number of metastases, degree of tumor differentiation according to Fuhrman, hemoglobin level, ECOG status, performance of CN and metastasectomy, and presence or absence of visceral metastases. In our modified model, only hemoglobin levels and ECOG status were included from the IMDC scale. We further divided patients with mRCC depending on our additional prognostic factors into 3 groups of favorable, intermediate and poor prognosis.

In the modified SOSh prognostic scale (Semyonov, Orlova, and Shirokorad), we calculated the score of prognostic factors for patients with mRCC.

The degree of tumor differentiation according to Fuhrman G1-2 – 0 points, G3 received 2 points. Depending on the time of metastases appearance, patients with synchronous metastases received 2 points, with metachronous metastases 0 points.

Patients with solitary or single metastases received 0 points, and patients with multiple metastases received 2 points. Patients with hemoglobin above 100 g/L were assigned 0 points, and those with hemoglobin below 100 g/L were assigned 2 points. If visceral metastases were present, 3 points were assigned, and 1 point was assigned for nonvisceral metastases. When metastasectomy was performed, patients were assigned 0 points, and in its absence 1 point. When CN was performed, mRCC patients were assigned 0 points and 1 point in its absence. Patients with ECOG 0-1 received 0 points, and with ECOG 2-4 received 2 points.

When scoring in our modified prognosis model, mRCC patients were categorized into 3 prognosis groups:

0-3 points – favorable prognosis;

4-8 points is an intermediate prognosis;

9-15 points – poor prognosis.

Thus, the favorable prognosis group in our modified model consisted of 107 (10.9%) mRCC patients, with 444 patients (45.2%) and 430 (43.9%) patients in the intermediate prognosis and poor prognosis groups, respectively.

In this study, the prognostic score of patients in the modified model in mRCC patients was calculated by adding up all the scores for individual factors. Each patient was scored from 0 to 15 points, patients were divided into 3 groups according to the prognostic score, and survival rates for each prognostic group were calculated. The Kaplan-Meier method showed that the higher the prognostic score, the lower the survival rates in mRCC patients.

In our modified prognostic groups, the 3- and 5-year OS rates in mRCC patients were 87.1% and 79.8%, 63.7% and 35.4%, 26.7% and 8.5% ($p<0.0001$). We also compared the OS rates of patients in the IMDC prognosis groups and in the modified groups.

At the same time, in our modified SOSh model we extended the intermediate prognosis group of mRCC patients by almost 6 months. In the case of poor prognosis, the OV indices did not differ among mRCC patients. The proposed prognosis scoring table differs from the existing ones (International Metastatic Renal Cell Carcinoma

Database Consortium) IMDC [32] by the increased number of evaluated prognostic factors, which in turn can lead to an increase in sensitivity and specificity of the new scale and improve the effectiveness of treatment and survival rates in patients with mRCC.

Forecast	IMDC (OV%)	SOSh (OV%)
Favorable	77.4-61.1	87.1-79.8
Intermediate	58.7-26.8	63.7-35.4
Poor	26.6-10.4	26.7-8.5

In a modified SOSh model in the poor prognosis group, we studied prognostic factors in mRCC patients and evaluated their influence on survival rates. In single- and multivariate analysis, the degree of tumor differentiation, number of metastases, ECOG status, hemoglobin level, and performance of HE were additional factors influencing the survival rates in mRCC patients with poor prognosis according to SOSh.

In our study, we showed that the group of poor prognosis is very variable and the use of our SOSh scale leads to the fact that patients with mRCC have to be differentiated. Currently, there is no clear consensus among researchers whether CN should be performed in poor prognosis mRCC patients in the setting of systemic therapy [77, 79]. The group of poor prognosis with high metastatic load is heterogeneous. Some authors recommend performing CN as the first stage [236, 241], while other researchers are strongly against this cytoreductive intervention [66, 232]. In our study, we found that there is no difference in survival rates in mRCC patients with poor prognosis based not only on the IMDC model but also on our modified SOSh model. Therefore, we divided the heterogeneous group of unfavorable prognosis of the modified SOSh model of mRCC patients into 2 subgroups: the group of poor and very poor prognosis and studied the effect of cytoreductive surgeries on survival rates. The conducted study revealed statistically significant differences in OS in the subgroup of poor prognosis in mRCC patients

depending on the performance of CN (p=0.02), but not in the subgroup of very poor prognosis (p=0.28). The 3- and 5-year OS rates of performing CN in the SOSh poor and very poor prognosis subgroups were 34.0% and 9.8%, 20.3% and 7.2%, respectively. In our study, we found no difference in survival rates in mRCC patients with poor and very poor SOSh prognosis when metastasectomy was performed (p=0.114 and p=0.093). In our opinion, CN is indicated in patients of the subgroup of poor prognosis according to SOSh, and in the group of very poor prognosis the first stage of complex treatment should be drug systemic therapy.

The currently used IMDC model was developed for mRCC patients receiving targeted therapy. We studied the efficacy of first-line systemic therapy in patients with mRCC depending on prognosis in the modified SOSh model and comparison with IMDC prognosis groups. Our study showed that mRCC patients who received first- and second-line targeted therapy in IMDC and SOSh prognosis groups showed no difference in treatment response. We found that patients given immunotherapy and combinations in the first and second line received a difference in treatment response in patients with intermediate and poor prognosis according to SOSh mRCC.

At carrying out of systemic therapy of 1 line in patients with mRCC in groups of prognosis according to IMDC and modified SOSh scale the difference in responses in patients at application of immunotherapy of intermediate (p=0.032 and p=0.011) and poor prognosis according to SOSh (p=0.037 and p=0.0079) was noted. When 2nd line systemic therapy was given to mRCC patients in the IMDC and modified SOSh prognosis groups, there was a difference in response in patients with poor prognosis according to SOSh with targeted therapy (p=0.014 and p=0.003); when using immunotherapy in the first and second line of intermediate (p=0.032 and p=0.011), (p=0.039 and p=0.017) and poor prognosis by SOSh (p=0.037 and p=0.0079), (p=0.042 and p=0.042).

Thus, our study showed that successfully selected first-line therapy will largely determine the prognosis and survival of mRCC patients, as well as reduce the economic costs of treatment.

According to the results of our study, the best treatment results in all lines of treatment were obtained with ICI and TKI. ICI demonstrated the highest rate of favorable outcomes even in tumors with a less favorable prognosis (non-small cell variant, low degree of differentiation). The tendency to decrease the frequency of favorable outcomes when switching to a new line of therapy is noteworthy. When patients are assigned to a new line of therapy, there is a decrease in the rate of complete and partial response, but the rate of progression also decreases. Therefore, it is necessary to carefully consider the choice of the first-line drug to stop or slow tumor progression. Patients with multiple metastases of RCC and lesions of more organs were significantly more likely to have an unfavorable outcome, which makes us think about the existence of "tumor burden", and may require revision of drug dosages taking into account their toxicity depending on the number of metastases. Despite the successes of modern systemic therapy, currently an important stage in the complex treatment of mRCC patients is the performance of metastasectomy for solitary and single metastases, which increases the OB indices. At the same time, it is necessary to take into account the use of palliative radiation therapy, which prolongs OS rates.

However, despite the numerous data available on the treatment of mRCC, there are a number of aspects of this problem directly related to the influence of various factors (clinical and laboratory, pathomorphological characteristics of the tumor, the number of affected organs, the time of occurrence and localization of metastases) on the rates of OS.

Thus, summarizing the results obtained, we concluded that the existing prognostic factors are incomplete, as the researchers did not take into account the time of occurrence, type, number and localization of metastases, tumor differentiation, duration of RFP, and cytoreductive surgeries in mRCC patients. After analyzing 981 mRCC patients, we extended the prognostic model. For the first time, we evaluated the influence of additional prognostic factors on survival rates and the frequency of objective responses and time after progression in mRCC patients in single- and multivariate analysis. In our opinion, it is necessary to take into account

clinical and laboratory, pathomorphological characteristics of the tumor, the number of affected organs, the time of occurrence and localization of metastases in mRCC patients before systemic therapy. The use of various cytoreductive therapies and their combinations influencing survival rates is relevant. We have shown that cytoreductive surgical interventions are effective even in patients with unfavorable prognosis of mRCC.

The prognosis scoring table proposed based on the results of our study differs from the existing models by the increased number of prognostic factors assessed, which may lead to an increase in the effectiveness of personalized systemic therapy and survival rates in patients with mRCC.

Thus, in our opinion, there is a need not only to modernize the IMDC prognosis model, but also to separate the group of poor prognosis for a more effective approach to cytoreductive surgical interventions and personalized systemic therapy in patients with mRCC.

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CONCLUSIONS

1. The 5-year overall survival (OS) rates in mRCC patients (n=981) depended on IMDC prognosis groups: the IMDC favorable, intermediate, and unfavorable prognosis groups were 61.1%, 26.8%, and 10.5%, respectively, with median overall survival rates of 72.2, 40.8, and 18.6 months, respectively ($p<0.0001$).

2. We studied 15 additional clinical and morphologic parameters in patients with mRCC not included in the IMDC prognostic scale. The statistical significance of such factors as the nature of metastases, the degree of tumor differentiation according to Fuhrman, CN and metastasectomy, the presence of visceral metastases was proved (significance of Cox model, a $p<0.0001$).

3. Inclusion of additional factors in the IMDC scale showed heterogeneity of the intermediate prognosis group. There was a statistically significant difference in 5-year OS in mRCC patients with 1 or 2 poor additional prognostic factors, with a median survival of 52 and 34 months, respectively ($p<0.0001$). In patients with single and multiple metastases, median OS rates were 52 and 24 months, respectively. The median OS for solitary metastases was not reached ($p<0.0001$). In patients with metachronous and synchronous metastases, the median OS was 43 and 27 months, respectively ($p<0.0001$).

4. The degree of tumor differentiation according to Fuhrman affects the OS rates of mRCC patients after surgical treatment of the primary tumor, with median OS at G1, G2 and G3 of 72.2, 41.6 and 22.1 months, respectively ($p<0.0001$).

5. A statistically significant difference in survival rates was found between mRCC patients with visceral and non-visceral metastases, with median OS of 71.8 and 30.2 months, respectively ($p<0.0001$).

6. There is a difference in OS in patients with mRCC depending on CN. The median 5-year OS was 36 months in patients who underwent CN and 11 months in patients who did not undergo CN ($p<0.0001$).

7. We found that when metastasectomy was performed, the median OS of mRCC patients was 49.6 months, respectively ($p<0.0001$), versus patients who did not undergo metastasectomy.

8. Based on the studied additional clinical and morphological parameters, a modified personalized prognosis model for mRCC SOSh patients was developed (Semenov, Orlova, Shirokorad). The sensitivity and specificity of the mathematical model were 89.3% and 80.5%.

9. It was found that the group of poor prognosis according to SOSh, unlike the IMDC model, is heterogeneous. For the first time, according to the SOSh prognostic model, the fourth additional group of very poor prognosis in mRCC patients was singled out. The median OS in the subgroup of poor and very poor prognosis according to SOSh was 29.5 and 12.3 months, respectively ($p<0.0001$).

10. It was found that CN is indicated in the group of poor prognosis according to SOSh ($p=0.02$) and inappropriate in patients with very poor prognosis ($p=0.28$). No differences in survival rates were found in patients with mRCC of poor and very poor prognosis according to SOSh when metastasectomy was performed ($p=0.114$ and $p=0.093$).

11. In the modified SOSh model, first-line systemic therapy with first-line systemic therapy was 2 times less frequent in contrast to the IMDC model in patients with favorable prognosis 67/166 and more frequent in patients with intermediate prognosis 347/269, respectively. No difference in response to first- and second-line targeted therapy was obtained in the IMDC and modified SOSh prognosis groups.

12. It has been shown that when systemic therapy is applied in the 2nd line in mRCC patients in the IMDC and modified SOSh prognosis groups, there is a difference in the responses in patients with poor prognosis according to SOSh in the target therapy ($p=0,014$ and $p=0,003$); when using immunotherapy in the first and second line of intermediate ($p=0.032$ and $p=0.011$), ($p=0.039$ and $p=0.017$) and poor prognosis by SOSh ($p=0.037$ and $p=0.0079$), ($p=0.042$ and $p=0.042$). The modified SOSh model showed a difference in response to immunotherapy, which may suggest effective application in the era of modern immuno-oncology drugs.

PRACTICAL RECOMMENDATIONS

The application of a personalized modified SOSh model for predicting the survival rates of patients with mRCC, taking into account the identified additional prognostic factors, is shown. This mathematical model can be used in practical healthcare to optimize the treatment of patients with mRCC. CN is indicated for patients in the subgroup of unfavorable prognosis according to SOSh. The modified SOSh model in mRCC patients showed a difference in the response to immunotherapy, which can speak about the effective application in the era of modern immuno-oncology drugs.

LIST OF ABBREVIATIONS AND SYMBOLS

ALP – alkaline phosphatase
CDKN2A/B – Cyclin-Dependent Kinase 2A
CI – relative risk
CN – cytoreductive nephrectomy
CR – complete response
CRP – C-reactive protein
CSS – cancer-specific survival
CT – computed tomography
ECOG – Eastern Cooperative Oncology Group
ESMO – European Society for Medical Oncology
ESR – erythrocyte sedimentation rate
HR – hazard ratio
IL-2 – interleukin-2
IFN-α – interferon-α
IMDC – International Metastatic Renal Cell Carcinoma Database Consortium
LDH – lactate dehydrogenase
mRCC – metastatic renal cell cancer
MRI – magnetic resonance tomography
MSKCC – Memorial Sloan-Kattering Cancer Center
mTOR – mammalian target of rapamycin
OS – overall survival
OSG – osteoscintigraphy
PBRM1 – regulation of transcription, DNA-templated
PDGFR-α – Platelet-Derived Growth Factor Receptor Alpha
PDGFR-β – Platelet-Derived Growth Factor Receptor Beta
PD-1 – programmed cell death PD-L1 – programmed death-ligand 1
PFS – progression-free survival

PR – partial response

RC – kidney cancer

RCC – renal cell cancer

RFP – reccurence-free period

RUSSCO – Russian Society of Clinical Oncology

SOSh – Semenov – Orlova – Shirokorad

SRE – skeletal related events

TKI – tyrosine kinase inhibitor

ULN – upper limit of normal

VEGF – Vascular Endothelial Growth Factor

VHL – Von Hippel-Lindau

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