Analysis of additional prognostic factors in patients with renal cancer metastases to the liver

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ABSTRACT

Purpose of the study. Was to identify additional prognostic factors in patients with renal cell cancer metastases to the liver influencing survival rates.

Patients and methods. In patients with renal cell cancer (RCC) metastases to the liver, a search for new prognostic factors affecting survival rates is needed. The retrospective analysis of data of 141 patients with liver metastases of RCC treated at the Moscow City Oncological Hospital No. 62 in Moscow and the City Clinical Oncological Dispensary (St. Petersburg) from 2006 to 2022 was carried out. Men prevailed (66.7 %), age 60–74 years in 51.1 %, low-differentiated tumors (56,0 %) and multiple metastases (83.7 %) were detected more often. The study investigated clinical and morphological prognostic factors influencing survival rates in patients with liver metastases of RCC. Statistical analysis was performed using Statistica 10.0 software packages (StatSoft, USA) by constructing Kaplan-Meier curves and survival tables, building a mathematical model of survival.

Results. The 3- and 5-year OS in patients with liver metastases of RCC (n = 141) was 42.4 % and 23.7 %, respectively, with a median OS of 22 months.

In a single-factor analysis in patients with renal cancer metastases to the liver, it was found that ECOG status (p < 0.001), histological subtype (p = 0.01) had a negative impact on survival rates, Fuhrman tumor differentiation (p < 0.001), type (p < 0.001) and number of metastases (p = 0.024), metastases to lymph nodes (p = 0.006), IMDC prognosis (p < 0.001), nephrectomy (p < 0.001) and metastasectomy (p = 0.0006).

In multivariate analysis, ECOG status [HR = 10.09 (95 % CI = 1.31–77], histological subtype [HR = 3,45 (95 % CI = 1.77–6.71], lymph node metastasis [HR = 1.93 (95 % CI = 1.21–3.07], hemoglobin level [HR = 2.44 (95 % CI=1.39–4.29], and undergoing nephrectomy [HR = 2.10 (95 % CI = 1.16–3.79] were additional predictors affecting OS rates in patients with liver metastases of RCC.

Conclusion. In our study, ECOG status, histological subtype, lymph node metastasis, hemoglobin level and nephrectomy were additional independent prognostic factors affecting AE rates in patients with RCC liver metastases. Further studies are needed to identify additional prognostic factors in patients with RCC liver metastases to improve the efficacy of personalized treatment.

Keywords: renal cell cancer, liver metastases, overall survival rate, prognostic factors

Анализ дополнительных факторов прогноза у больных с метастазами рака почки в печень

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РЕЗЮМЕ

Цель исследования. Выявить дополнительные прогностические факторы у больных с метастазами рака почки в печень, влияющие на показатели выживаемости.

Пациенты и методы. У пациентов с метастазами в печень почечноклеточного рака (ПКР) необходим поиск новых прогностических факторов, влияющих на показатели выживаемости. Проведен ретроспективный анализ данных 141 пациента с метастазами в печень ПКР, получавших лечение в ГБУЗ «Московская городская онкологическая больница № 62 Департамента здравоохранения города Москвы», г. Москвы и СПбГУЗ «Городской клинический онкологический диспансер», г. Санкт-Петербург с 2006 по 2022 гг., из которых преобладали мужчины (66,7 %), возраст 60–74 года, у 51,1 %, чаще выявлены низкодифференцированные опухоли (56,0 %) и наличие множественных метастазов (83,7 %). В исследовании изучены клинико-морфологические факторы прогноза, влияющие на показатели выживаемости у больных с метастазами в печень ПКР. Статистический анализ проводился с использованием пакетов программного обеспечения Statistica 10.0 (StatSoft, США) посредством построения кривых Каплана-Мейера и таблиц дожития, построение математической модели дожития.

Результаты. 3- и 5-летняя общая выживаемость (ОВ) у больных с метастазами в печень ПКР ($n = 141$) составила 42,4 и 23,7 % соответственно, при этом медиана ОВ составила 22 месяца.

В однофакторном анализе у больных с метастазами рака почки в печени выявлено, что отрицательное влияние на показатели выживаемости оказывали статус по ECOG ($p < 0,001$), гистологический подтип ($p = 0,01$), степень дифференцировки опухоли по Fuhrman ($p < 0,001$), тип ($p < 0,001$) и количество метастазов ($p = 0,024$), метастазы в лимфатические узлы ($p = 0,006$), прогноз по IMDC ($p < 0,001$), проведение нефрэктомии ($p < 0,001$) и метастазэктомии ($p = 0,0006$).

При многофакторном анализе ECOG статус [HR = 10,09 (95 % ДИ = 1,31–77], гистологический подтип [HR = 3,45 (95 % ДИ = 1,77–6,71], метастазы в лимфатические узлы [HR = 1,93 (95 % ДИ = 1,21–3,07], уровень гемоглобина [HR = 2,44 (95 % ДИ = 1,39–4,29], а также проведение нефрэктомии [HR = 2,10 (95 % ДИ = 1,16–3,79] были дополнительными предикторами влияющими на показатели ОВ у пациентов с метастазами в печень ПКР.

Заключение. В нашем исследовании ECOG статус, гистологический подтип, метастазы в лимфатические узлы, уровень гемоглобина и проведение нефрэктомии были дополнительными независимыми прогностическими факторами, влияющими на показатели ОВ у пациентов с метастазами в печень ПКР.

Ключевые слова: почечноклеточный рак, метастазы в печень, общая выживаемость, прогностические факторы

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INTRODUCTION

Renal cell carcinoma of the kidney (RCC) accounts for about 2 % of the total number of diagnosed and deceased cancers worldwide [1]. The 5-year survival in patients with metastatic RCC (mRCC) is 12 % [2, 3], and 25–30 % of patients with RCC have metastatic disease at initial diagnosis [4, 5]. The liver is one of the common locations for metastasis and affects 20 % of patients with mRCC [6]. Unfortunately, the development of liver metastases is considered a poor prognostic factor and is often associated with low survival rates [7, 8]. The median progression-free survival in patients with RCC was significantly shorter in the presence of liver metastases, and the median overall survival in patients was less than 12 months [9–10]. For a long time, the selection of patients with mRCC was based on the IMDC prediction model, which is now insufficient in the era of immuno-oncological drugs. In our study, we analyzed additional prognostic factors in patients with kidney cancer metastases to the liver.

The purpose of the study was to identify additional prognostic factors in patients with kidney cancer metastases to the liver that affect survival rates.

Table 1. Patients' characteristics (*n* = 141)	
Characteristic	Number of patients (*n* (%))
Sex: male female	94 (66.7) 47 (33.3)
Age, years: 18−44 45−59 60−74 ≥75	9 (6.4) 54 (38.3) 72 (51.1) 6 (4.3)
Histological type: clear-cell carcinoma non-clear-carcinoma	118 (83.7) 23 (16.3)
Differentiation grade: G1 G2 G3	19 (13.5) 43 (30.5) 79 (56.0)
ECOG status: 0 1 2 3	5 (3.5) 43 (30.5) 46 (32.6) 47 (33.3)
Number of metastases: solitary single multiple	5 (3.5) 18 (12.8) 118 (83.7)
IMDC prognosis: favorable intermediate poor	26 (18.4) 40 (28.4) 75 (53.2)
Metastasis type: metachronous synchronous	66 (46.8) 75 (53.2)
Prior nephrectomy: yes no	117 (83.0) 24 (17.0)
Normal hemoglobin Anemia	70 (49.6) 71 (50.4)

3-year OS: 42.4 %   5-year OS: 23.7 %

Number at risk

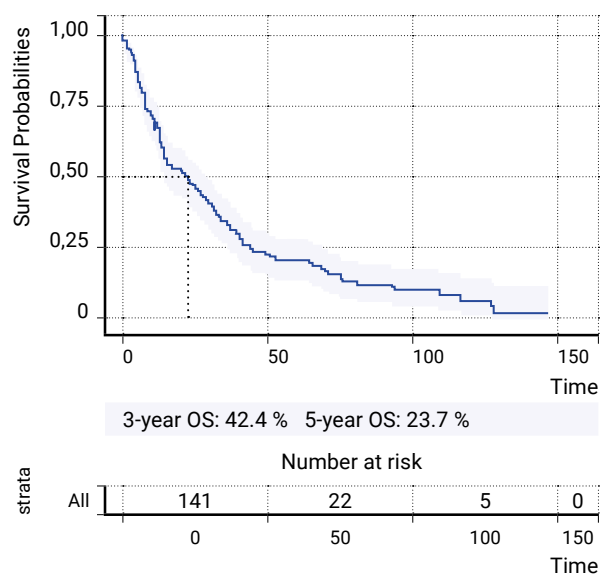| strata				
All	141	22	5	0
	0	50	100	150
				Time

Fig. 1. OS rate of patients with liver metastases of RCC (*n* = 141)
Note: Median of the OS was 22 months

PATIENTS AND METHODS

A retrospective analysis of the data of 141 patients with liver metastases of RCC treated at the Moscow City Oncological Hospital No. 62 in Moscow and the City Clinical Oncological Dispensary (St. Petersburg) from 2006 to 2022 was carried out. Males (66.7 %) predominated, the age of 60–74 years in 51.1 %, low-grade tumors were more often detected (56.0 %) and the presence of multiple metastases (83.7 %). The study examined the clinical and morphological prognostic factors affecting survival rates in patients with liver metastases of RCC.

Statistical analysis

Statistical analysis was carried out using Statistica 10.0 software packages (StatSoft, USA) by constructing Kaplan-Meyer curves and survival tables, and constructing a mathematical survival model. All patients received systemic antitumor therapy. Detailed characteristics of the patients are given in Table 1.

3-year OS: 75 % 68.1 % 30.4 % 6.4 %
5-year OS: 75 % 43.8 % 14.1 % 0 %

Number at risk

ECOG				
0	5	3	1	0
1	43	14	3	0
2	46	5	4	0
3	47	0	0	0
	0	50	100	150
				Time

A Log - rank *p* < 0.0001

3-year OS: 73.7 % 45.3 % 18.5 %
5-year OS: 68.4 % 17.8 % 7.4 %

Number at risk

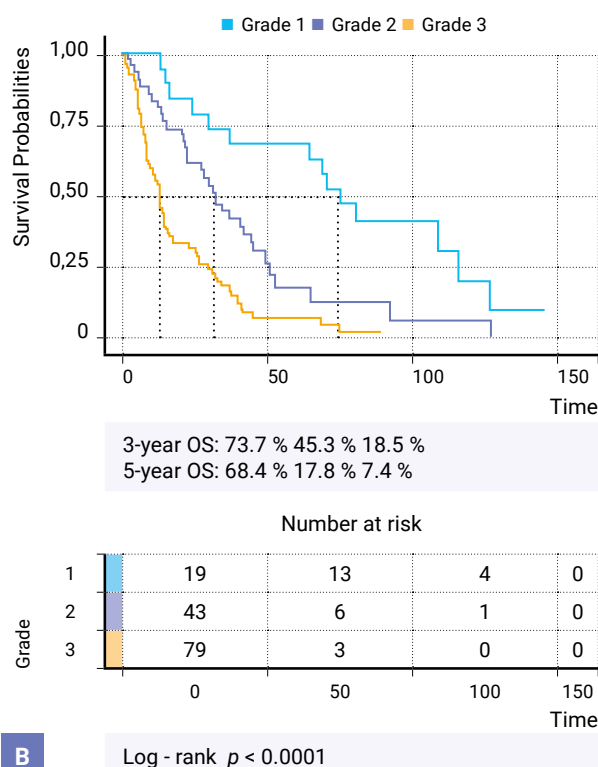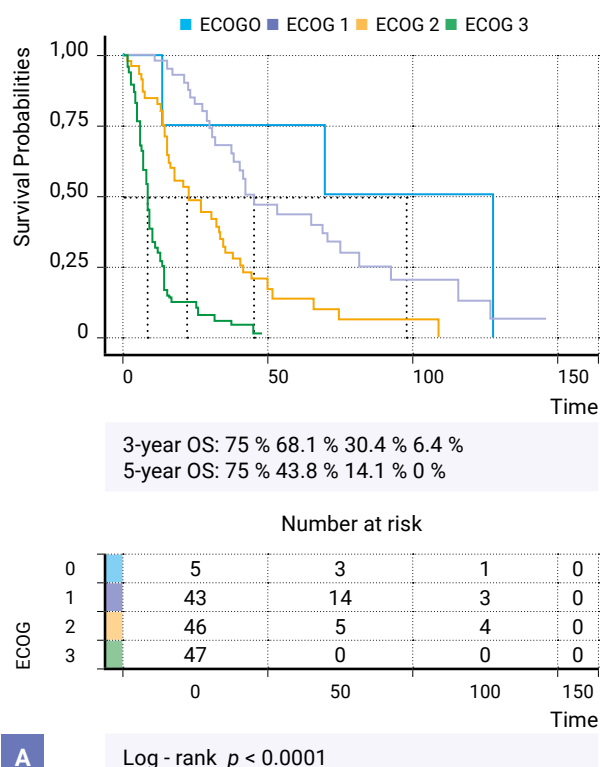| Grade				
1	19	13	4	0
2	43	6	1	0
3	79	3	0	0
	0	50	100	150
				Time

B Log - rank *p* < 0.0001

Fig. 2. Overall survival (OS) in patients with RCC liver metastases depending on ECOG status (a) and Fuhrman tumor differentiation (b) (*n* = 141)
Note: the median OS for ECOG 0.1.2 and 3 was 98.6, 45, 22 and 7.9 months, and for G1, G2 and G3 it was 74.8, 31.9 and 13 months, respectively

Table 1 shows that low-grade tumors (56 %), multiple metastases (83.7 %), and an unfavorable IMDC prognosis (53.2 %) were the most common.

Patient data was consolidated in the form of spreadsheets and analyzed using the Statistica 12 for Windows program. Life expectancy was calculated from the date of diagnosis to the date of last observation or death. Survival was assessed using the Kaplan-Mayer method, survival differences were determined using the log-rank test; Cox regression analysis was used to exclude factors that do not have independent prognostic significance. A single-factor analysis was used to determine whether there were statistically significant differences between two or more groups in one independent variable. A multifactorial analysis was used to determine the effect of several factors on the dependent variable. The analysis of OS indicators in patients with nmPCR was carried out depending on clinical and morphological parameters. The analysis of the risk ratio of an event at a certain point in time t in one group compared with another group (Hazard Ratio (HR)) was performed.

STUDY RESULTS

The clinical and morphological characteristics of the patients are presented in Table 1. The study was dominated by 90 men (66.7 %). 75 (53.2 %) patients had an unfavorable prognosis according to IMDC, while 79 (56 %) were diagnosed with low-grade tumors. Multiple metastases were detected in 118 (83.7 %) patients. These data indicate that the group of patients with nmPCR has a pronounced metastatic load.

In a one-factor analysis in patients with kidney cancer metastases in the liver, it was revealed that ECOG status ($p < 0.001$), histological subtype ($p = 0.01$), degree of tumor differentiation according to Fuhrman ($p < 0.001$), type ($p < 0.001$) and number of metastases ($p = 0.024$), lymph node metastases ($p = 0.006$), IMDC prognosis ($p < 0.001$), nephrectomy ($p < 0.001$) and metastasectomy ($p = 0.0006$) (Table 1, Fig. 2–6).

In multivariate ECOG analysis, the status [HR = 10.09 (95 % CI = 1.31–77], histological subtype [HR = 3.45 (95 % CI = 1.77–6.71], lymph node metas-
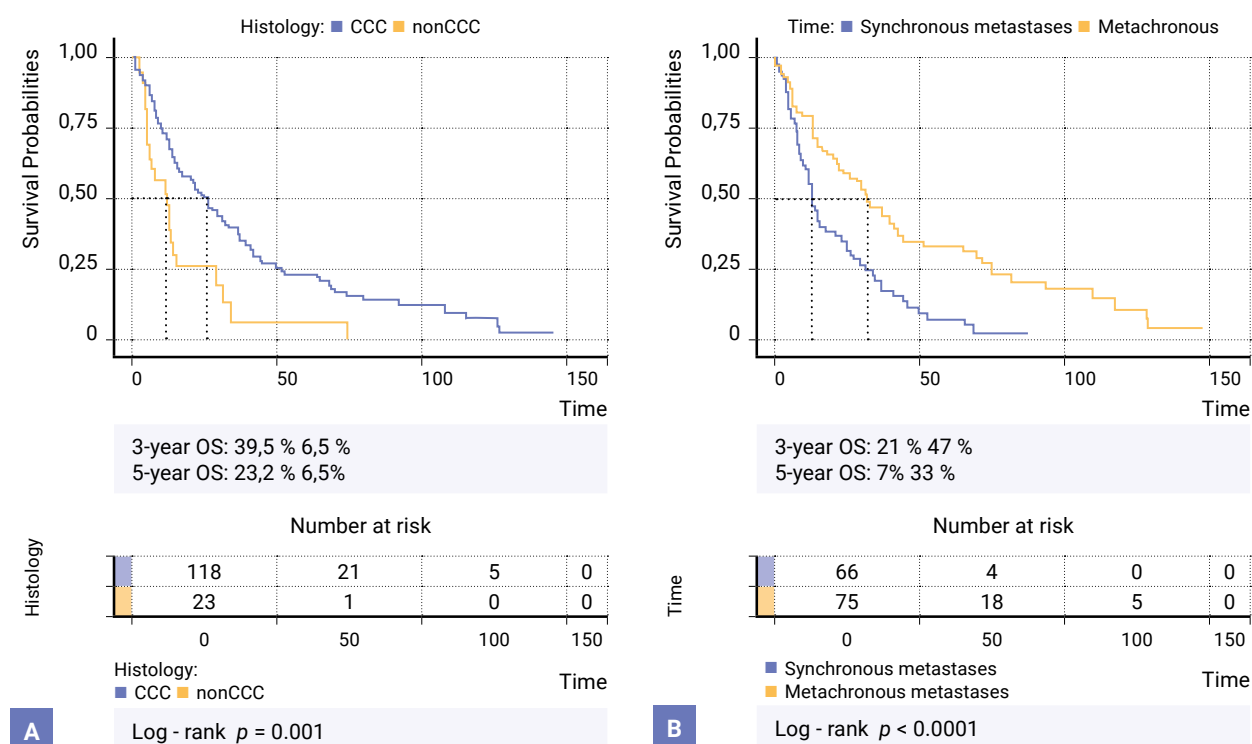

Fig. 3. Overall survival (OS) in patients with RCC liver metastases as a function of histologic subtype dependency (a) and time of metastasis occurrence (b) (n = 141)
Note: the median OS for clear-cell and non-clear-cell RCC was 26.3 and 12 months, respectively, and for synchronous and metachronous metastases, 13.2 and 31.4 months, respectively

3-year OS: 60 % 55.6 % 30.2 %
5-year OS: 60 % 34.8 % 16.6 %

Number at risk

Number				
	5	3	2	0
	18	6	1	0
	118	13	2	0
	0	50	100	150

Number: ■ Solitary ■ Single
■ Numerous

A   Log - rank *p* = 0.024

3-year OS: 42.1 % 22.8 %
5-year OS: 27.7 % 9.9 %

Number at risk

In				
	85	18	5	0
	56	4	0	0
	0	50	100	150

Лу: ■ In met (-)
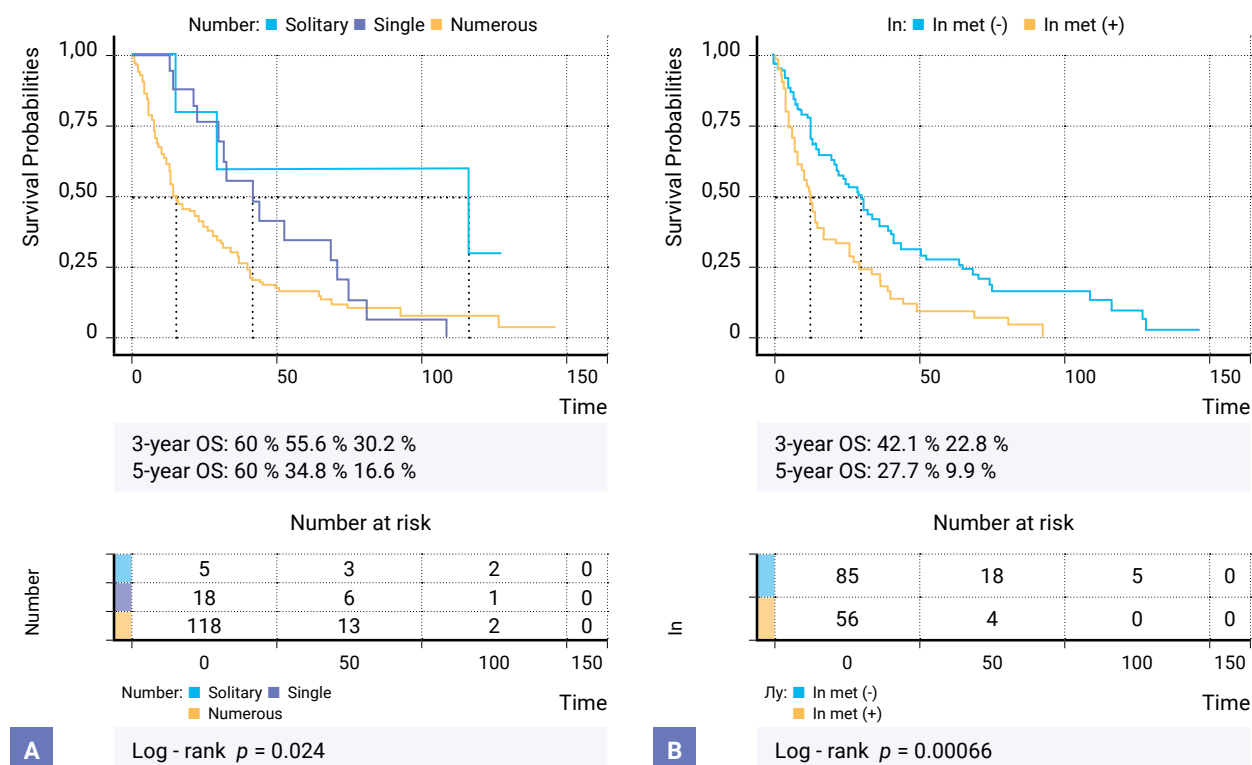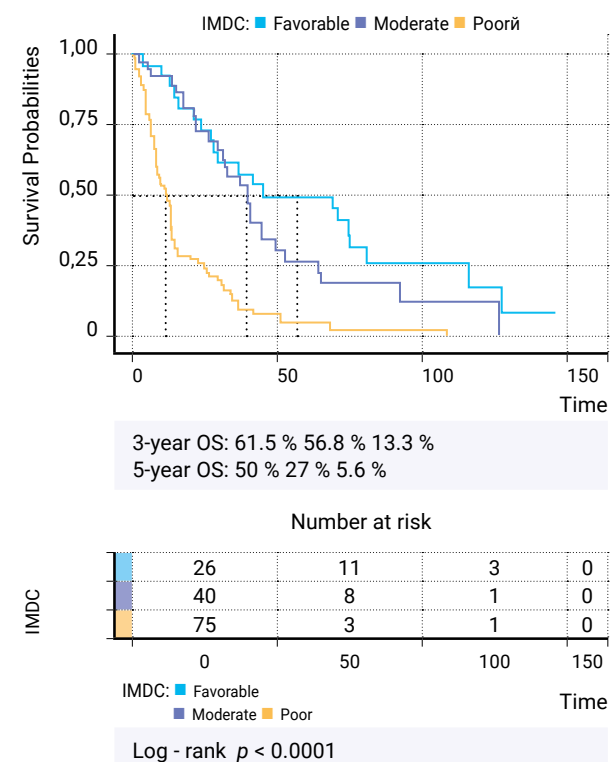■ In met (+)

B   Log - rank *p* = 0.00066

Fig. 4. Overall survival (OS) in patients with liver metastases of RCC depending on the number of metastases (a) and with and without lymph node metastases (b) (*n* = 141)
Note: the median OS in patients with solitary, single, and multiple metastases was 116.6, 41.8, and 15.5 months, respectively, and in the absence and presence of lymph node metastases, 30.9 and 13.4 months, respectively

3-year OS: 61.5 % 56.8 % 13.3 %
5-year OS: 50 % 27 % 5.6 %

Number at risk

IMDC				
	26	11	3	0
	40	8	1	0
	75	3	1	0
	0	50	100	150

IMDC: ■ Favorable
■ Moderate ■ Poor

Log - rank *p* < 0.0001

tases [HR = 1.93 (95 % CI = 1.21–3.07], hemoglobin level [HR = 2.44 (95 % CI = 1.39–4.29], as well as nephrectomy [HR = 2.10 (95 % CI = 1.16–3.79] were additional factors that had an independent negative effect on OS in patients with liver metastases of RCC (Table 2).

DISCUSSION

RCC is a highly vascularized tumor and is prone to the appearance of distant metastases [11]. About 30 % of new cases are metastatic at the time of diagnosis [12]. The liver is one of the most common locations of RCC metastases, including 23.6 % of newly diagnosed cases of metastatic RCC and is associated with poor overall survival rates [13]. Despite the fact that treatment strategies for mRCC have improved significantly over the past decade,

Fig. 5: Overall survival (OS) in patients with RCC liver metastases according to IMDC prognosis (*n* = 141)
Note: the median OS for favorable, intermediate, and poor IMDC prognosis was 57.1, 39.8, and 12 months, respectively

there is still no consensus on the optimal clinical strategy for the treatment of liver metastases of RCC [14–16]. A prognostic model for liver metastases of RCC would be very useful for personalized treatment [17].

In our work, we have shown that the IMDC model, which was developed to analyze the forecast of mRCC [18, 19] is insufficient. In our study, ECOG status, histological subtype, lymph node metastases, hemoglobin levels, and nephrectomy were important prognostic factors in RCC liver metastases. Most of these predictors are not taken into account in modern forecasting models. It is interesting to note that the IMDC prognosis, type and number of metastases were not prognostic predictors in patients with RCC with liver metastases.

This study also has some limitations. First of all, because of the retrospective nature. Further multi-center studies are needed to determine the clinical, pathomorphological and molecular prognostic factors in patients with kidney cancer metastases to the liver.

CONCLUSIONS

In our study, ECOG status, histological subtype, lymph node metastases, hemoglobin level, and nephrectomy were additional independent prognostic factors affecting OS in patients with liver metastases of RCC. Further studies are needed to identify additional prognostic factors in patients with liver RCC metastases in order to increase the effectiveness of personalized treatment.
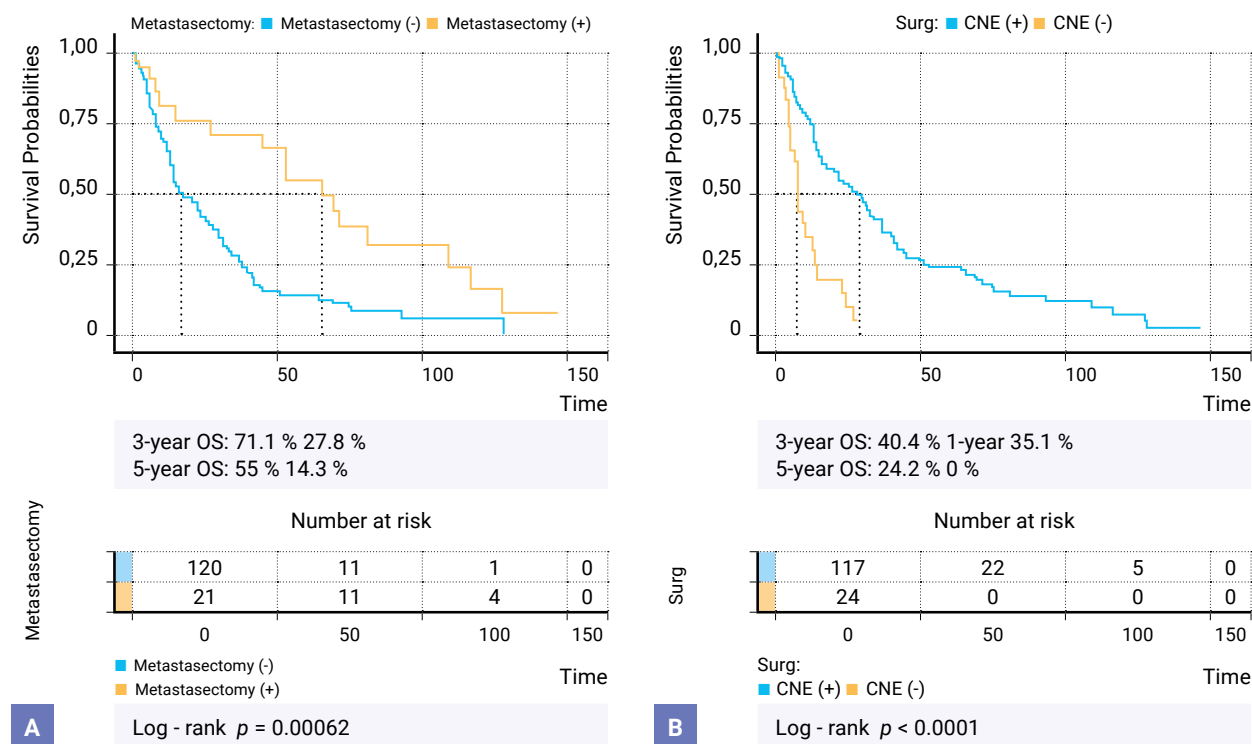

Fig. 6. Overall survival (OS) in patients with RCC liver metastases when metastasectomy is performed (a) and with and without CNE (b) (n = 141)
Note: the median OS in the absence and performance of metastasectomy was 17.5 and 65.2 months, respectively, and in the absence and performance of CNE was 29.3 and 8.1 months, respectively

Table 2. Predictive factors for overall survival rate for patients with liver metastases of RCC (*n* = 141) (single-factor and multifactor analysis)

Factor	Number of patients (%)	Hazard ratio (95 % confidence interval)	
		Univariate test	Multivariate test
ECOG status: 1 2 3	5 (3.5) 43 (30.5) 46 (32.6) 47 (33.3)	– 1.66 (0.49−5.61, *p* = 0.417) 4.07 (1.1913.98, *p* = 0.026) 13.99 (4.0048.89, *p* < 0.001)	– 1.16 (0.18−7.51, *p* = 0.880) 2.37 (0.34−16.68, *p* = 0.388) 10.09 (1.31−77.63, *p* = 0.026)
Histological type: clear-cell carcinoma non-clear-carcinoma	118 (83.7) 23 (16.3)	– 2.20 (1.36−3.58, *p* = 0.001)	– 3.45 (1.77−6.71, *p* < 0.001)
Differentiation grade: G1 G2 G3	19 (13.5) 43 (30.5) 79 (56.0)	– 2.33 (1.21−4.46, *p* = 0.011) 5.24 (2.79−9.83, *p* < 0.001)	– 1.70 (0.69−4.22, *p* = 0.251) 1.59 (0.61−4.11, *p* = 0.342)
Metastasis type: metachronous synchronous	66 (46.8) 75 (53.2)	– 0.45 (0.31−0.67, *p* < 0.001)	– 1.13 (0.66−1.96, *p* = 0.649)
Lymph nodes metastases: present absent	85 (60.3) 56 (39.7)	– 1.90 (1.31−2.77, *p* = 0.001)	– 1.93 (1.21−3.07, *p* = 0.006)
Hemoglobin: yes − normal no − anemia	70 (49.6) 71 (50.4)	– 3.04 (2.05−4.50, *p* < 0.001)	– 2.44 (1.39−4.29, *p* = 0.002)
Prior nephrectomy: yes no	117 (83.0) 24 (17.0)	– 3.57 (2.14−5.97, *p* < 0.001)	– 2.10 (1.16−3.79, *p* = 0.014)
Metastasectomy: yes no	120 (85.1) 21 (14.9)	– 0.39 (0.23−0.68, *p* = 0.001)	– 0.58 (0.26−1.30, *p* = 0.186)

Note: the table only presents factors with prognostic significance

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