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PREDICTORS OF LOCAL RECURRENCE OF RENAL CELL CANCER. OUR EXPERIENCE

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Abstract

Risk factors for renal cell cancer (RCC) recurrence, including its local form, include stage and high Fuhrman grading system score, regional lymph node involvement, microvascular invasion, tumor necrosis, positive surgical margin, and sarcomatoid or rhabdoid tumor differentiation. **Objective.** The study analyzes data from Moscow Research Oncological Institute named by PA Herzen to determine the predictors of local recurrence of kidney cancer based on the data from surgically treated patients with local recurrent RCC. **Material and Methods.** We analyzed retrospectively data from 87 patients who were divided into 2 groups: 1-st, patients with detected local recurrence of kidney cancer (n=43), and 2-nd, control group (n=44). The following predictors were evaluated: tumor size, tumor histotype, tumor stage, Fuhrman grading system, surgical margin status, tumor necrosis, sarcomatoid and rhabdoid changes, microvascular invasion, hemorrhage and invasion of collecting system components (CSS), renal capsule, and perirenal cellular tissue and primary treatment. **Results.** The risk of local recurrence was higher in the primary tumor, over 40 mm in diameter (OR=5.8, p<0.001), as well as microvascular invasion and focal hemorrhage (OR=15.1, p=0.001 and OR=3.3, p=0.008, respectively). Both univariate and multivariate analyses showed a negative effect on the risk of local RCC recurrence only for tumor necrosis (OR=15.4, p<0.001 and OR=53.6, p=0.002, respectively) and high Fuhrman grade (OR=10.9, p=0.042 and OR=5.7, p=0.032, respectively). The most significant predictors of local renal cancer recurrence are tumor necrosis (p<0.001), microvascular invasion (p=0.019), positive surgical margin (p=0.009), and high Fuhrman grade (p=0.04). High Fuhrman grade (3–4) of malignancy (HR=1.9, p=0.042), tumor diameter (HR=1.0, p=0.054), positive surgical margin (HR=3.5, p=0.001), and tumor necrosis (HR=2.3, p=0.029) were found to be the most significant factors influencing 5-year local recurrence-free survival rate. **Conclusion.** The course of renal cell cancer is determined by multiple interrelated and independent prognostic factors.

Key words: renal cell carcinoma, local recurrence, predictors of local recurrence; risk factors of local recurrence; prognostic factors of local recurrence; predisposing factors of local recurrence; local recurrence-free survival rate.

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ПРЕДИКТОРЫ МЕСТНОГО РЕЦИДИВА РАКА ПОЧКИ. НАШ ОПЫТ

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Аннотация

К факторам риска рецидива почечно-клеточного рака (ПКР), в том числе его локальной формы, относят стадию и высокую степень злокачественности по Фурману, поражение регионарных лимфатических узлов, микрососудистую инвазию, некроз опухоли, положительный хирургический край, а также саркоматоидную или рабдоидную дифференцировку опухоли. **Целью исследования** является определение предикторов местного рецидива рака почки на основании анализа данных пациентов, перенесших хирургическое лечение по поводу местного рецидива ПКР на базе МНИОИ им. П.А. Герцена. **Материал и методы.** Нами был проведен ретроспективный анализ данных 87 пациентов, которые были разделены на 2 группы: 1 – пациенты с местным рецидивом рака почки (n=43), 2 – контрольная группа с безрецидивным течением заболевания (n=44). Были оценены следующие характеристики: размер опухоли, гистотип опухоли, стадия заболевания, степень злокачественности опухоли по Фурману, состояние хирургического края, некроз опухоли, саркоматоидные и рабдоидные изменения, микроваскулярная инвазия (МВИ), кровоизлияния и инвазия компонентов собирательной системы (КСС), капсулы почки и околопочечной клетчатки, а также характер первичной операции. **Результаты.** Вероятность возникновения местного рецидива была выше в группе пациентов с диаметром первичной опухоли более 40 мм (OR=5,8, p<0,001), а также при наличии МВИ и участков кровоизлияния (OR=15,1, p=0,001 и OR=3,3, p=0,008 соответственно). В ходе как однофакторного, так и многофакторного анализа был доказан негативный эффект риска местного рецедива ПКР только у таких показателей, как некроз опухоли (OR=15,4, p<0,001 и OR=53,6, p=0,002 соответственно) и высокая степень злокачественности по Фурману (OR=10,9, p=0,042 и OR=5,7, p=0,032 соответственно). Наиболее значимыми предикторами местного рецидива рака почки являются некроз опухоли (p<0,001), МВИ (p=0,019), положительный хирургический край (ПХК) (p=0,009) и высокая степень злокачественности по Фурману (p=0,04). Высокая степень злокачественности по Фурману (3–4-я степень) (HR=1,9, p=0,042), диаметр опухоли (HR=1,0, p=0,054), ПХК (HR=3,5, p=0,001) и некроз опухоли (HR=2,3, p=0,029) являются наиболее значимыми факторами, влияющими на 5-летнюю локальную безрецидивную выживаемость. **Выводы.** Течение почечно-клеточного рака определяется множеством взаимосвязанных между собой, а также рядом независимых друг от друга прогностических факторов.

Ключевые слова: почечно-клеточный рак; местный рецидив; предикторы местного рецидива; факторы риска местного рецидива; прогностические факторы местного рецидива; предрасполагающие факторы местного рецидива; локальная безрецидивная выживаемость.

Introduction

Risk factors for renal cell cancer (RCC) recurrence, including its local form, include stage and high Fuhrman grading system score, regional lymph node involvement, microvascular invasion, tumor necrosis, positive surgical margin, and sarcomatoid or rhabdoid tumor differentiation [1]. Several studies have attempted to prove that tumor histotype is an independent predictor of disease outcome; but all histological variants of kidney cancer have been able to behave aggressively [2–4].

Objective. The study analyzes data from Moscow Research Oncological Institute named by PA Herzen to determine the predictors of local recurrence of kidney cancer based on the data from surgically treated patients with local recurrent RCC.

Material and Methods

We analyzed retrospectively data from 87 patients who underwent nephrectomy or kidney resection for RCC between 1999 and 2018. Patients of both sexes were included in the study and divided into 2 groups:

1, patients with detected local recurrence of kidney cancer (n=43), and 2, control group of patients with relapse-free disease (n=44).

In the main group, most patients (74.4 %) underwent the first operation outside the inpatient department of Moscow Research Oncological Institute, named by PA Herzen. The finished histological slides were reviewed by a pathomorphologist from the institute to determine several indices: tumor histotype, tumor stage, Fuhrman grading system, surgical margin status, tumor necrosis, sarcomatoid and rhabdoid changes, microvascular invasion, hemorrhage and invasion of collecting system components (CSS), renal capsule, and perirenal cellular tissue. Tumor size and the nature of the primary surgery were also important criteria for assessing the likelihood of local recurrence. The main instrumental method of diagnosing local RCC recurrence was multispiral computed tomography with intravenous contrast, analyzed also by a single specialist.

None of the patients received pre- or postoperative therapy. We defined local recurrence as a tumor nodule detected after radical removal of a primary tumor of the same histological type in the bed of the removed tumor after renal resection [5]. A tumor mass in the renal bed [6], as well as involvement of regional lymph nodes and ipsilateral adrenal gland were taken as local recurrence after nephrectomy [7].

Univariate and multivariate Cox regression models were used to identify predictors of recurrence. The $p<0.05$ was significant. For statistical analysis, local recurrence-free survival (L-RFS) was calculated as the time from surgery to setting of local recurrence of kidney cancer. Statistical analysis was performed using IBM SPSS v.26.0 software. L-RFS was estimated using the Kaplan-Meier method.

Results

We analyzed data from 87 patients operated for renal cell cancer between 2000 and 2018. Table 1 presents the clinical and pathomorphological characteristics of the patients. The study included patients of both sexes. The mean age was 57.6 years (26 to 76 years). The average follow-up period was 8 years (9 months to 20 years). For the underlying disease, patients underwent both surgical and non-surgical treatment. The mean primary tumor size was 56.3 mm (range 10–130 mm). The major histotype was the clear cell RCC in both groups.

In the first group local recurrence was mainly represented in the grades 3 and 4 malignancy patients (69.8 %). In the local relapsed RCC group, the signs of tumor necrosis, microvascular invasion, sarcomatoid and rhabdoid features, hemorrhage and positive surgical margin were more common. On average, the local recurrence of kidney cancer was diagnosed 32.7 months (2.7 years) after surgery.

Table 2 presents the most frequent locations of local recurrence after major surgery in patients with established local recurrence. In 5 patients undergone radiofrequency ablation for a tumor, 100 % local recurrence occurred in the previously performed ablation, in the tumor itself.

In the study, we also evaluated the effect of the above-described indices on the likelihood of local RCC recurrence. A univariate analysis identified the most likely risk factors for local RCC recurrence. The risk of local recurrence was higher in the primary tumor, over 40 mm in diameter (OR=5.8, $p<0.001$), as well as the pathomorphological features of microvascular invasion and focal hemorrhage in tumor tissue (OR=15.1, p=0.001 and OR=3.3, p=0.008, respectively). Both single-factor and multivariate analyses showed a negative effect on the risk of local RCC recurrence only for tumor necrosis (OR=15.4, $p<0.001$ and OR=53.6, p=0.002, respectively) and high Fuhrman grade (OR=10.9, p=0.042 and OR=5.7, p=0.032, respectively). Table 3 presents the results of the comparative analysis.

Stepwise logistic regression algorithm showed the most significant factors for the probability of local RCC recurrence (Table 4). Based on these data, the most significant predictors of local renal cancer recurrence are tumor necrosis ($p<0.001$), microvascular invasion (p=0.019), positive surgical margin (p=0.009), and high Fuhrman grade (p=0.04).

Based on these results, we created a prognostic model (Fig. 1) and found a significant effect of the above criteria on the probability of local recurrence of kidney cancer (AUC=0.947). Logistic regression was performed with stepwise inclusion of predictors. Model parameters: Sensitivity 83.7 %, Specificity 90.9 %, $R^2=0.656$. The significance of the model is $p<0.001$, $\chi^2 = 58\ 922$.

The next step was to assess the effect of the criteria on the 5-year local recurrence-free survival (L-RFS)

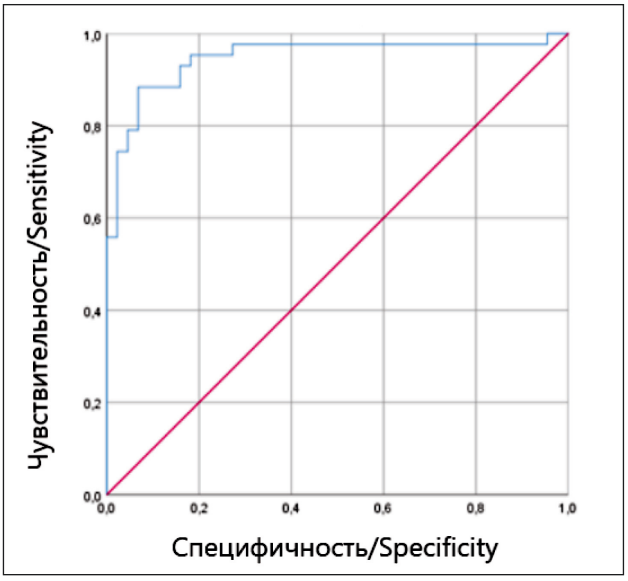

Fig. 1. ROC-curve
Рис. 1. ROC-кривая

Table 1/Таблица 1

The clinical and pathomorphological characteristics

Клинические и патоморфологические данные пациентов

Variables/Показатель		Number of cases/ Число случаев	1st group/ 1–я группа (n=43)	2nd group/ 2–я группа (n=44)
Sex/Пол	Male/Мужчины	45 (51.7 %)	24 (55.8 %)	21 (47.7 %)
	Female/Женщины	42 (48.3 %)	19 (44.2 %)	23 (52.3 %)
Age, years/Возраст, лет	Mean/Среднее значение	57.6	59.2	56.3
BMI/ИМТ	Mean/Среднее значение	29.3	30.5	28.7
Clinical T–stage/ Клиническая Т–стадия	cT1a/1b	54 (62.1 %)	18 (41.9 %)	36 (81.8 %)
	cT2a/2b	20 (23 %)	14 (32.5 %)	5 (11.4 %)
	cT3a/3b/3c	11 (12.6 %)	9 (20.9 %)	3 (6.8 %)
	cT4	2 (2.3 %)	2 (4.7 %)	–
Treatment/ Лечение	Partial nephrectomy/ Резекция почки	49 (56.3 %)	15 (34.9 %)	34 (77.3 %)
	Radical nephrectomy/ Нефрэктомия	33 (38 %)	23 (53.5 %)	10 (22.7 %)
	RFA/ РЧТА	5 (5.7 %)	5 (11.6 %)	–
Tumor size, mm/ Размер опухоли, мм	≤40	40 (46 %)	10 (23.3 %)	30 (68.2 %)
	≥40	47 (54 %)	33 (76.7 %)	14 (31.8 %)
Histological type/ Гистотип опухоли	ccRCC	76 (87.4 %)	37 (85.9 %)	39 (88.6 %)
	Papillary/	5 (5.7 %)	2 (4.7 %)	3 (6.8 %)
	Chromophobe/	4 (4.6 %)	2 (4.7 %)	2 (4.6 %)
	Other/	2 (2.3 %)	2 (4.7 %)	–
Fuhrman grade/ Степень злокачественности по Фурману	1–2	49 (56.3 %)	13 (30.2 %)	36 (81.8 %)
	3–4	38 (43.7 %)	30 (69.8 %)	8 (18.2 %)
Kidney capsule invasion/ Инвазия капсулы почки	Yes/Да	51 (58.6 %)	23 (53.5 %)	28 (63.6 %)
	No/Нет	36 (41.4 %)	20 (46.5 %)	16 (36.4 %)
Tumor necrosis/ Некроз опухоли	Yes/Да	39 (44.8 %)	32 (74.4 %)	7 (15.9 %)
	No/Нет	48 (55.2 %)	11 (25.6 %)	37 (84.1 %)
Microvascular invasion/ Микроваскулярная инвазия	Yes/Да	22 (25.3 %)	20 (46.5 %)	2 (4.5 %)
	No/Нет	65 (74.7 %)	23 (53.5 %)	42 (95.5 %)
Sarcomatoid and rhabdoid features/ Саркоматоидные и рабдоидные изменения	Yes/Да	15 (17.2 %)	15 (34.9 %)	–
	No/Нет	72 (82.8 %)	28 (65.1 %)	44 (100 %)
Tumor hemorrhage/ Кровоизлияние в опухоли	Yes/Да	39 (44.8 %)	25 (58.1 %)	14 (31.8 %)
	No/Нет	48 (55.2 %)	18 (41.9 %)	30 (68.2 %)
UCS invasion/ Инвазия КСС	Yes/Да	6 (6.9 %)	3 (7 %)	3 (6.8 %)
	No/Нет	81 (93.1 %)	40 (93 %)	41 (93.2 %)
Perirenal fat invasion/ Инвазия паранефральной клетчатки	Yes/Да	12 (13.8 %)	6 (14 %)	6(13.6 %)
	No/Нет	75 (86.2 %)	37 (86 %)	38 (86.4 %)
Surgical margin/ Хирургический край	PSM/ПХК	16	14 (32.6 %)	2 (4.5 %)
	NSM/НХК	71	29 (67.4 %)	42 (95.5 %)
Time to recurrence/ Время до рецидива	≤12 months (continued tumor growth)/ ≤12 мес (продолженный рост)	–	21 (48.8 %)	–
	≥12 months (true recurrence)/ ≥12 мес (истинный рецидив)	–	22 (51.2 %)	–

Note: BMI – body mass index; RFTA – radiofrequency thermoablation; ccRCC – clear cell renal cell carcinoma; CCC – collecting system components; PSM – positive surgical margin; NSM – negative surgical margin.

Примечания: ИМТ – индекс массы тела; РЧТА – радиочастотная термоабляция; скПКР – светлоклеточный почечно-клеточный рак; КСС – компоненты собирательной системы; ПХК – положительный хирургический край; НХТ – негативный хирургический край.

Table 2/Таблица 2

The most frequent locations of local recurrence
Наиболее частая локализация местных рецидивов

Localization/Локализация	Detection frequency/ Частота рецидива
Tumor bed/Ложе опухоли	19 (44 %)
Kidney bed/Ложе почки	18 (41.9 %)
Lymph nodes/Лимфатические узлы	8 (18.6 %)
Ipsilateral adrenal gland/Ипсилатеральный надпочечник	4 (9.3 %)
Renal pedicle/Почечная ножка	6 (14 %)
Vena cava inferior/Нижняя полая вена	2 (4.7 %)
Surrounding organs (liver, mesentery of the colon, spleen)/ Окружающие органы (печень, брыжейка, селезенка)	10 (23.3 %)

Table 3/Таблица 3

The effect on the risk of local RCC recurrence
Влияние на риск местного рецидива ПКР

Variables/Показатель		Univariate analysis/ Однофакторный анализ				Multivariate analysis/ Многофакторный анализ			
		OR	95 % CI	P–Value	χ^2	OR	95 % CI	P–Value	χ^2
Sex/Пол	M/M	1,4	0,6–3,2	0,451	0,57	1,4	0,6–3,2	0,762	0,09
	F/Ж	0,7	0,3–1,7	0,451	0,57	0,7	0,3–1,7	0,762	0,09
Age/ Возраст	<45	0,2	0,0–13,8	0,462	2,45	0,2	0,0–13,8	0,462	0,54
	>45	4,8	0,1–323,3	0,462	2,45	4,8	0,1–323,3	0,462	0,54
BMI/ ИМТ	<25	0,6	0,2–2,0	0,425	0,64	0,2	0,0–6,8	0,372	0,80
	>25	1,6	0,5–4,9	0,425	0,53	5,0	0,1–169,9	0,372	0,80
Treatment/ Лечение	PN	<0,001	–	0,999	0	–	–	0,999	0
	RN	<0,001	–	0,999	0	–	–	0,999	0
	RFA	–	–	–	11,38	–	–	–	0,03
Tumor size, mm/ Размер опухоли, мм	<40	0,2	0,1–0,4	<0,001	12,19	0,2	0,0–3,2	0,257	1,29
	>40	5,8	2,3–14,7	<0,001	13,46	5,0	0,3–79,5	0,257	1,29
Histological type/ Гистотип опухоли	ccRCC	0,7	0,2–2,3	0,508	0,44	0,6	0,0–12,4	0,733	0,12
	other	1,5	0,4–5,2	0,508	0,44	1,7	0,1–35,9	0,733	0,12
Fuhrman grade/ Степень злокачественности по Фурману	G1,2	1,7	0,2–16,4	0,667	1,87	5,7	1,2–27,7	0,032	0,11
	G3,4	10,9	1,1–108,6	0,042	1,98				
Kidney capsule invasion/ Инвазия капсулы почки		0,8	0,3–1,9	0,600	0,28	0,2	0,0–2,4	0,189	1,72
Tumor necrosis/Некроз опухоли		15,4	5,3–44,3	<0,001	25,57	53,6	4,3–671,1	0,002	9,52
Microvascular invasion/ Микроваскулярная инвазия		15,1	3,2–70,7	0,001	11,91	12,1	0,8–179,8	0,070	3,28
Tumor hemorrhage/ Кровоизлияние опухоли		3,3	1,4–7,9	0,008	6,97	0,7	0,0–12,7	0,794	0,07
UCS invasion/Инвазия КСС		1,4	0,3–6,7	0,671	0,18	0	0,0–1,2	0,062	3,48
Perirenal fat invasion/Инвазия паранефральной клетчатки		1,5	0,5–4,6	0,530	0,40	8,4	0,4–169,0	0,166	1,92
PSM/ПХК		10,1	2,1–48,0	0,004	7,44	20,8	2,1–202,6	0,009	6,82

Note: BMI – body mass index; PN – partial nephrectomy; RN – radical nephrectomy; RFA – radio frequent ablation; ccRCC – clear cell renal cell carcinoma; UCS – urinary collecting system; PSM – positive surgical margin.

Примечание: ИМТ – индекс массы тела; РП – резекция почки;НЭ – нефрэктомия; РЧТА – радиочастотная термоабляция; скПКР – светлоклеточный почечно-клеточный рак; КСС – компоненты собирательной системы; ПХК – положительный хирургический край.

Table 4/Таблица 4

The most significant factors for the probability of local RCC recurrence

Наиболее значимые факторы, определяющие вероятность развития местного рецидива ПКР

Variables/Показатель	OR	95 % CI	P-Value	χ^2
Tumor necrosis/Некроз опухоли	10.6	2.9–39.5	<0.001	12.43
Microvascular invasion/ Микроваскулярная инвазия	9.1	1.4–56.7	0.019	5.54
PSM/ПХК	20.8	2.1–202.6	0.009	6.82
Fuhrman grade/ Степень злокачественности по Фурману	6.1	1.8–21.2	0.004	8.19

Note: PSM – positive surgical margin.

Примечание: ПХК – положительный хирургический край.

Table 5/Таблица 5

Influence of factors on 5-year local recurrence-free survival rate

Влияние показателей на 5-летнюю локальную безрецидивную выживаемость

Variables/Показатель		Results/Результаты		
		HR	95 % CI	P-Value
Sex/Пол		0.9	0.5–1.8	0.799
BMI/ИМТ		0.9	0.9–1.0	0.011
Tumor size/Размер опухоли		1.0	1.0–1.0	0.054
Treatment/ Лечение	RN/НЭ	–	–	1.000
	PN/РП	0.4	0.1–1.2	0.106
	RFA/РЧТА	23.5	4.7–117.3	<0.001
Histological type/Гистотип опухоли		0.9	0.5–1.5	0.599
Fuhrman grade/Степень злокачественности по Фурману		1.9	1.0–3.7	0.042
Kidney capsule invasion/Инвазия капсулы почки		0.4	0.2–0.9	0.033
Tumor necrosis/Некроз опухоли		2.3	1.1–4.7	0.029
Microvascular invasion/Микроваскулярная инвазия		2.0	0.7–5.9	0.207
Sarcomatoid and rhabdoid features/ Саркоматоидные и рабдоидные изменения		1.8	0.7–4.4	0.189
Tumor hemorrhage/Кровоизлияние опухоли		1.0	0.4–2.4	0.969
UCS invasion/Инвазия КСС		1.0	0.3–3.4	0.955
Perirenal fat invasion/Инвазия паранефральной клетчатки		2.0	0.8–5.1	0.133
PSM/ПХК		3.5	1.7–7.3	0.001

Note: BMI – body mass index; PN – partial nephrectomy; RN – radical nephrectomy; RFA – radio frequent ablation; UCS – urinary collecting system; PSM – positive surgical margin.

Примечание: ИМТ – индекс массы тела; РП – резекция почки; НЭ – нефрэктомия; РЧТА – радиочастотная термоабляция; КСС – компоненты собирательной системы; ПХК – положительный хирургический край.

of patients treated for RCC (Table 5). In a stepwise analysis, high Fuhrman grade (3–4) of malignancy (HR=1.9, p=0.042), tumor diameter (HR=1.0, p=0.054), positive surgical margin (HR=3.5, p=0.001), and tumor necrosis (HR=2.3, p=0.029) were found to be the most significant factors influencing 5-year local recurrence-free survival rate. The nature of the primary treatment was also found to determine the timing of local recurrence-free survival. Thus, radiofrequency ablation affected the index negatively (HR=23.5, p<0.001).

Discussion

Researchers consider the likelihood of local recurrence of kidney cancer after primary treatment of RCC mainly in terms of overall recurrence-free survival. Unfortunately, only a few studies have addressed the impact of the above clinical and pathomorphologic parameters on the likelihood of developing a directly local RCC recurrence. In 2019, a team from Spain showed, in a retrospective multivariate analysis of 153 patients, the influence of histological factors such as microvascular invasion (p=0.001) and tumor necrosis (p=0.0001) on the likelihood of developing local recurrence. Therefore, the indices were identified as independent predictors of local renal tumor recurrence [8].

A Mayo Clinic study confirmed the tumor size as an anatomical factor in local RCC recurrence. The authors state that each centimeter of tumor size increases the

likelihood of local recurrence (p<0.05). After several calculations, they concluded that a primary tumor sized 4 cm compared to that sized 1 cm has a 2.52 times higher risk of local recurrence [9].

In evaluating the effect of treatment on the rate of local RCC recurrence, a meta-analysis published by an American group shown higher survival without local recurrence for surgical treatment of kidney cancer compared with thermoablation (98.9 % vs 93.0 %). However, the authors make some clarification: When multiple thermoablation sessions were performed, the differences for surgical and ablative techniques were not significant [7]. A study from the Mayo Clinic proved the equivalence of these therapies in the treatment of local RCC recurrence. In renal cancer of cT1a stage, the 5-year local recurrence-free survival rates were 97.7 % (96.7–98.6), 95.9 % (92.3–99.6) and 95.9 % (92.3–99.6) for renal resection, RFA, and cryoablation, respectively. For cT1b stage RCC, the rates for kidney resection and cryoablation were 91.6 % (88.2–95.1) and 92.7 % (83.5–100), respectively [10].

The most studied and controversial marker of local recurrence of renal cell cancer is the condition of the surgical margin. A recent meta-analysis showed for cT1-T2 stage tumors that enucleation is at least as good as the standard renal resection in terms of PSM and local recurrence at 24 months follow-up [11]. The authors also stressed lack of accepted definition of «positive surgical margin» and «tumor recurrence», which markedly reduces the significance of the results. Bernhard et al. analyzed the results of 809 kidney resections performed in 8 European and American centers. During the follow-up (mean 27 months), 26 patients (3.2 %) experienced local tumor recurrence. Researchers found a direct effect of PSM on the risk of local RCC recurrence (p<0.01) [12]. In 2016, Shah confirmed these findings in a retrospective multicenter study including data from 1240 kidney resections and stressed PSM as a reliable predictor of recurrence (95 % CI 2.75–20.34, p<0.001) only in highly aggressive (pT2–3a or Fuhrman grade 3–4) tumors with no effect on localization of recurrence (local/remote) [13]. A group from Argentina studied a role of Fuhrman grade along with surgical margin status on the likelihood of local RCC recurrence. In a multivariate analysis, PSM and high grade of renal cancer malignancy (Fuhrman grade 3 or 4) were identified as independent predictors of local RCC recurrence (HR=12.9, 95 % CI 1.8–94, p=0.011/HR=38.3, 95 % CI 3.1–467, p=0.004, respectively) [14].

In 2017, an Israeli team proved a direct effect of surgical margin status on the likelihood of locoregional cancer recurrence after nephrectomy for primary kidney cancer [15]. From 612 patients, a local RCC recurrence developed in 50 during the follow-up (average, 65 months). PSM was found to determine the lowest 5-year survival without local recurrence (93 % vs 45 %; p<0.001). Multivariate analysis confirmed these results: PSM was associated with a significantly increased risk of local tumor recurrence (HR 4.8; 95 % CI 2–11.6; p=0.01).

In contrast to these results, an American group in a retrospective analysis of 1994 cases confirmed the relative importance of surgical margin status on the development of true local recurrence. They detected clinically local recurrence of kidney cancer in 30 patients, with 9 cases (0.5 %) of true primary tumor recurrence, with only one patient with PSM. Several reasons can explain the local recurrence against a negative surgical margin. One is the so-called «false negative surgical margin», that is, malignant tissue outside the tumor boundaries defined during surgery, such as within the peritumoral vessels, which leads to incomplete resection [16]. X.S. Chen et al. described foci of tumor tissue extending 3 mm beyond the tumor pseudo-capsule [17]. The researchers concluded that the histological nature and tumor malignancy, as well as its sarcomatoid and rhabdoid changes, have greater prognostic value for local tumor recurrence than the surgical margin status [11,16, 18].

The course of renal cell cancer is determined by multiple interrelated and independent prognostic factors, which are included in many prognostic models. A comparative analysis of the most popular and widely used predictive models presented in a recent prospective collaborative study by a group of scientists from USA and Canada [19]. To reduce the probability of local postoperative recurrence of the disease, a thorough preoperative examination is of primary importance. To improve the effectiveness of primary treatment and the recurrence-free survival, oncourologists should personalize the search and evaluation of predisposing factors for the development of local recurrence and then select the best treatment. Precise search of morphological, immunohistochemical, and biochemical markers in the surgical material can improve the early postoperative management of the patients in the future. For example, one can determine the need for adjuvant therapy to reduce the risk of local RCC recurrence. Currently clinicians rely on retrospective prediction tools to guide patient care and clinical trial selection. But as shown in a study by a group from USA and Canada, using prospectively collected adjuvant trial data, existing RCC prediction models were validated and demonstrated a sharp decrease in the predictive ability of all models compared with their previous retrospective validations. So they recommend prospective validation of any predictive model before implementing it into clinical practice and clinical trial design [19].

Conclusion

The literature considers the development of the local recurrence of kidney cancer in the aspect of the general recurrence-free survival rate. This is the main problem for revealing and the complete analysis of the predisposing factors. We believe the new search for markers specific for local RCC recurrence is important for optimization of RCC treatment.

We plan to develop an accessible multiparametric prognostic model including objective clinical, laboratory-instrumental, and pathomorphological data to predict the local RCC recurrence. The nomogram will be of great practical value for optimization of both treatment and postoperative management of RCC patients. The latter includes the decision to provide adjuvant therapy to a group of patients selected by the nomogram.

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