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Prognostic factors of overall survival in renal cancer patients – single oncological center study

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Introduction. The clinical course of renal cancer remains difficult to predict. Attempts to appoint new independent prognostic factors (IPFs) and comparisons of already identified ones among populations are inevitable to develop more effective prognostic instruments. The aim of this study was to evaluate IPFs of overall survival in a given population of patients with renal cancer.

Materials and methods. Retrospective analysis of 148 patients with renal cancer treated at the Oncological Institute in Cracow from 2000 to 2007 was performed. Mean follow–up was 51 months. Using the log–rang test, a group of clinicopathological and biochemical features was analyzed in respect to their influence on overall survival. Results were presented as Kaplan–Meier curves. Final identification of IPFs was made by multivariate Cox regression analysis.

Results. Overall survival rate at 1, 2, and 5–year follow–up was 58.8%, 38.2%, and 21.4%, respectively. The set of identified IPFs consisted of performance status, smoking history, hemoglobin concentration, anatomical staging, tumor grade, and the presence of microvascular invasion. It was confirmed that only nephrectomy increases significantly overall survival.

Conclusions. Apart from smoking history, the role of all other IPFs identified in our study is well documented in the literature. Smoking history seems to be a new IPF with strong negative impact on survival in patients with RCC.

Key Words: prognostic factors ‹› renal cancer ‹› population study ‹› overall survival

INTRODUCTION

The course of renal cancer is highly unpredictable. Patients with small tumor may have distant metastasis with adverse prognosis, while patients with metastasis to lymph nodes, after nephrectomy may live more than five years [1, 2].

In numerous studies over last decade, new clinicopathological features expected to support prognostication in various groups of patients with RCC (i.e. before or after treatment, with or without metastatic disease) were considered [3]. Among them some clinical (symptoms, performance status), histological (tumor subtype, histological grade, microvascular invasion), biochemical (hemoglobin, calcium concentrations, LD serum activity), molecular, and cytogenetic variables turned out to provide additional prognostic information, as they correlate with long term follow–up outcomes reported in previously performed studies [4, 5, 6]. Based on these data, and independent prognostic factors (IPFs), new scoring systems assessing the clinical course of renal cancer were proposed [7].

Among the variety of major scoring systems referring to renal cancer, it is remarkable how different sets of IPFs they may use, depending on aspects of

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a prognosis they are about to assess and groups of patients they apply to. For instance Karakiewicz nomogram (KN) predicts 1–, 2–, 5–, and 10–year of cancer specific survival for the patients with renal cancer in all stages. This post–surgery nomogram uses as IPFs: TNM classification (2002), tumor size, tumor grade according to Fuhrman, histological tumor sub–type, patient's age, and presence of symptoms [8]. Another scoring system, assessing overall survival of the patients with metastatic renal cancer disease was proposed by Motzer. The IPFs set according to this model included: Karnofsky performance status, hemoglobin concentration, serum calcium concentration, serum lactate dehydrogenase activity (LDH), and time passed from diagnosis to treatment [9].

One of the merits of the current prognostic tools is the fact that their efficacy is measurable. It is expressed by prediction accuracy (PA), a value that falls within the range from 100% (an ideal confidence of the prediction) to 50% (what represents the outcome probability assessment equal to a toss of a coin) [3]. This allows to compare scoring systems to one another and to evaluate their prognostic efficacy for different populations (external validation). It is stressed in the literature that the discriminating ability of a particular scoring systems vary among populations, depending on ethnic dissimilarities and quality of treatment (diagnostic and therapeutic standards functioning in local healthcare system, i.e. methods of histopathological examination, agents available in adjuvant therapy) [10–14]. It is necessary to confirm the usefulness of the IPFs defined previously and prognostic tools in various populations of patients [3, 15].

MATERIAL AND METHOD

Retrospective analysis of 148 patients with renal cancer, treated at the Oncological Institute in Krakow in years 2000–2007, was performed. Mean age of the analyzed group of patients was 59.6 years (range: 33 to 79), mean observation time was 51 months (range 5 to 109 months). Staging (according to TNM scale, version for the year 2002) was estimated based on computer tomography with contrast and lung radiogram [16]. Basing on the same clinical data, the patients were divided according to anatomic stages (TNM grouping according to AJCC, 2010).

In case of suspicion of metastasis to bones or the central nervous system, additional imaging studies were performed. Kidney removal was performed according to standard criteria and was accompanied by local lymphadenectomy, if they were palpable during surgery or enlarged in imaging studies. After surgery, patients were followed up no less than every

Table 1. *Population characteristic*

Variable	is	n	%
Sex	Male	102	68.9
	Female	46	31.1
Smoking history	Yes	103	69.6
	No	45	30.4
Symptoms	Pain	87	59.2
	Haematuria	29	19.9
	Tumour	4	2.7
	Weakness	8	5.4
	Loss of body weight	5	3.4
	No symptoms	33	22.3
Metastasis location	Lungs	52	35.1
	Liver	18	12.2
	To bones	52	35.1
	To brain	6	4.1
	To lymph nodes	80	54.1
	Other	8	5.4
Feature T acc. to TNM v. 2002	T1	17	14.3
	T2	29	24.4
	T3a	45	37.8
	T3b	22	18.5
	T4	6	5.0
Feature N	N0	18	18.4
	N1	80	81.6
Feature M	M0	13	10.1
	M1	116	89.9
Fuhrman grade	I	7	6.6
	II	29	27.4
	III	52	49.0
	IV	18	17.0
Histological subtype	Clear cellular	34	46.6
	Papillary	7	9.6
	Sarcomatoid	5	6.8
	Chromophobe	11	15.1
	Collecting duct	1	1.4
	Unclassified	15	20.5
Microvascular invasion (MVI)	No	105	70.9
	Yes	43	29.1
Nephrectomy	No	25	16.9
	Yes	123	83.1
Chemiotherapy	No	105	70.9
	Yes	43	29.1
Immunotherapy	No	134	90.5
	Yes	14	9.5
Targeted therapy	No	132	89.2
	Yes	16	10.8
Hormonotherapy	No	124	83.8
	Yes	24	16.2
Radiotherapy	Bones	50	33.8
	Lungs	1	0.7
	Brain	4	2.7
	Local recurrence	10	6.8
Symptomatical treatment	No	98	66.2
	Yes	50	33.8

Variable	Value	n	%
ECOG Performance status	0	9	7.0
	1	87	68.0
	2	23	18.0
	3	5	3.9
	4	4	3.1
AJCC Anatomic stage	I	19	14.5
	II	18	13.7
	III	20	15.3
	IV	74	56.5

six months. In the post–surgery surveillance, apart from history and physical examinations, blood analysis (morphology, biochemical analysis) and imaging studies (chest x–ray, abdominal cavity ultrasound and CT) were performed. In case of bone pain, either bone x–ray or scintigraphy was performed. In case of the lack of technical possibilities of surgical removal of kidney or due to the patients' general state, they were qualified for immunotherapy or other types of treatment. The patient's cause of death was designated based on death certificate, the leading urologist inscription, or interview with the family members.

Statistical analysis

Continuous quantitative variables were characterized using arithmetic mean, median, range, and standard deviation. Categorical variables were reported as proportions expressed in percentages. Patients were divided into cohorts in respect to each variable. The cumulative overall survival rates in subsequent years of follow–up were calculated for the entire group and for each cohort separately. In the same way, the Kaplan–Meier cumulative survival probability curves were plotted. In the univariate analysis, using log–rank test, differences in overall survival between cohorts and their statistical significances were assessed. Factors influencing overall survival were included in multivariate Cox regression analysis, which gave final identification of independent prognostic factors in the analyzed group of patients. Basic statistical significance level used in the paper was $p < 0.05$. The characteristics of the analyzed group are presented in table 1.

RESULTS

The 1, 2, 3, 4, and 5–year cumulative survival probability in the entire group of patients was 58.8%, 38.2%, 32.7%, 29.1%, and 21.4%, respectively. Our study comprised patients with RCC in all stages. However, the majority of them (89.9%) were metastatic. Most of the patients in our group died due to the cancer, and cancer specific and overall survival did not significantly change in value. All clinicopathological and biochemical data were evaluated for their influence on overall survival (OS). There were no differences in survival rates in respect to sex (5–year survival: F–19.8%, M–27.1% $p = 0.3068$), whereas analysis of age distribution by the use "k–mean" method revealed two points of highest morbidity: 51.5 and 69 years.

Results of univariate analysis describing the influence of each variable on overall survival in our group of patients were gathered in tables 2, 3, 4, and 5. Selected factors were also presented as Kaplan Meier curves.

Univariate analysis

Prognostic factors from history and physical examination (Table 2).

Table 2. *Overall survival rate [%] according to factors from history and physical examination*

Feature		n	Years of follow-up					Significance
			1st	2nd	3rd	4th	5th	
ECOG Performance Status	0	9	88.9	88.9	88.9	88.9	63.5	p <0.001
	1	87	64.4	39.6	32.4	29.9	20.2	
	2	23	26.1	8.7	8.7	4.3	4.3	
	3+4*	9	0.0	0.0	0.0	0.0	0.0	
Lumbar Pain	No	60	70.0	51.2	45.9	42.3	29.2	p <0.05
	Yes	87	50.6	28.7	24.1	20.5	16.5	
Symptoms Presence	Symptomatic	115	51.3	32.2	26.1	22.5	17.5	p <0.001
	Asymptomatic	33	84.8	59.5	56.2	52.9	36.4	
Cigarettes Smoking	No	103	65.0	46.5	39.6	35.5	27.9	P <0.01
	Yes	45	44.4	18.7	16.4	14.0	9.4	

*Groups with 3 and 4 points of ECOG PS were combined due to small quantities

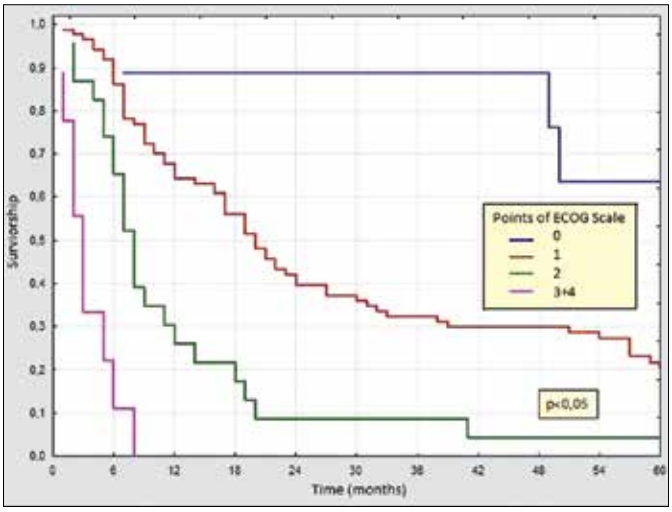

Figure 1. *Kaplan-Meier overall survivorship curves according to ECOG performance status. (Due to small number groups of patients in 3rd and 4th stage were combined).*

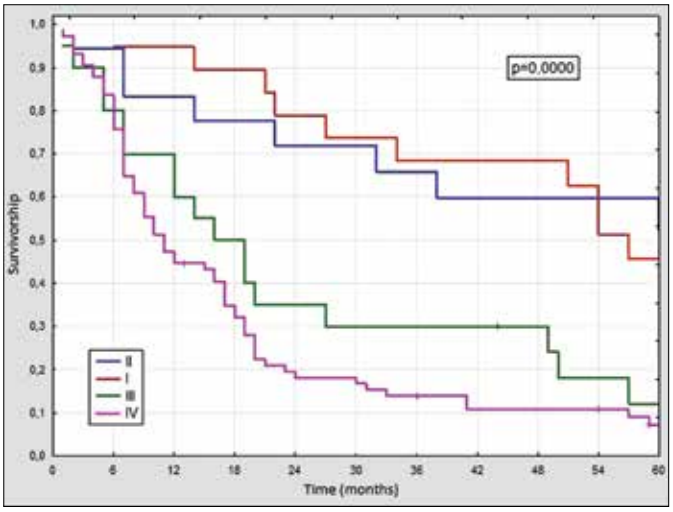

Figure 2. *Kaplan-Meier overall survivorship curves according to AJCC anatomic stage, 2010 (p <0.001).*

In this group of factors ECOG performance status most substantially influenced overall survival (Figure 1). Patients with no clinical symptoms at the moment of diagnosis had much better prognosis than those with symptoms (p <0.001). Among symptoms reported in patient history, only lumbar pain at side of the affected kidney significantly affected overall survival (p <0.01). Other symptoms: overall weakness (p = 0.1138), body weight loss (p = 0.0559), hematuria (p=0.5242), and palpable tumor (p = 0.1289) were not statistically significant. Smoking history was a negative predictor of overall survival in the investigated group (p <0.001).

Prognostic factors from imaging (Table 3)

Comparing survival rates in groups subdivided according to TNM features and AJCC tumor stages (2010) substantial differences in overall survival rates were found (p <0.001) (Figure 2). Tumor extent (T feature acc. to TNM) delineated on the base of CT scanning was the only data obtained from imaging examinations, affecting overall survival with lower statistical significance (p <0.03). Exact localization of distant metastasis did not differ the overall survival (lungs (p = 0.4955), liver (p = 0.0519), bones (p = 0.0559), central nervous system (p = 0.4035), and others (p = 0.2543)].

Table 3. *Overall survival rate according to TNM features and AJCC anatomic stage*

Feature		n	Years of follow-up					Significance
			1st	2nd	3rd	4th	5th	
Feature T in TNM	T1	17	88.2	52.9	47.1	47.1	32.2	p = 0.0386
	T2	29	75.9	50.6	39.7	36.1	28.1	
	T3a	45	53.3	33.3	28.6	23.8	20.8	
	T3b	22	54.5	31.8	27.3	27.3	10.9	
	T4	6	16.7	16.7	16.7	16.7	.	
Feature N in TNM	N0	18	83.3	71.4	65.5	65.5	58.9	p <0.005
	N1	80	52.5	23.8	18.9	16.1	9.2	
Feature M in TNM	M0	13	100	84.6	84.6	84.6	68.4	p <0.005
	M1	116	55.2	33.2	26.0	21.4	15.4	
AJCC Anatomic stage. 2010	I	18	94.7	78.9	68.4	68.4	45.6	p <0.001
	II	19	83.3	71.8	65.8	59.8	52.4	
	III	20	60.0	35.0	30.0	30.0	12.0	
	IV	74	44.6	18.1	13.9	10.8	7.2	

Table 4. *Overall survival rate according to histological findings*

Feature		n	Years of follow-up					Significance
			1st	2nd	3rd	4th	5th	
Fuhrman grade	1+2*	36	77.8	57.6	57.6	51.9	38.1	p = 0,0002
	3	52	69.2	36.5	26.4	24.2	15.4	
	4	18	27.8	11.1	11.1	11.1	11.1	
Microvascular invasion	No	105	61.0	45.7	38.9	33.9	25.3	p <0.001
	Yes	43	53.5	19.5	17.0	17.0	11.3	

*Groups 1 and 2 were combined due to small quantities

Prognostic factors from histological examination (Table 4)

Statistical analysis did not show influence of histological subtype of the tumor on overall survival in the examined group of patients (type clear–cellular (p = 0.9026), papillary (p = 0.4180), sarcomatoid (p = 0.8634), chromophobe (p = 0.9933), collecting duct (p = 0.2933), and other (p = 0.9846). However, the correlation of Fuhrman grade and overall survival rate was statistically significant (p <0.002) (Figure 3). Statistical significance referring to microvascular invasion in blood vessels was also noticed (p <0.04).

Table 5. *Overall survival rate according to nephrectomy*

Nephrectomy performed:	n	1 year	2 years	3 years	4 years	5 years
No	25	16.0	12.0	12.0	6.0	0.0
Yes	123	67.5	43.5	36.8	33.5	25.3

Prognostic factors of overall survival in relation to the applied treatment

Patients with advanced renal cancer at the moment of diagnosis should undergo nephrectomy only if technically possible. By analysis of the influence of surgery on overall survival, it was shown that the group of patients after surgery lives much longer, based on 5–year observations (p <0.002) (Table 5/ Figure 4). The influence of nonsurgical treatment of the patients with advanced renal cancer was also evaluated. In the period between 2000 and 2007, (if nephrectomy was not possible) supplementary or main treatment consisted of cytokines (immunotherapy) administration. Unfortunately, no prolongation of patients' life as a result of immunotherapy was noted (p = 0.85). Other alternative treatment methods (chemotherapy (p = 0.2844), hormonotherapy (0.5914), radiotherapy (for all radiated organs (p <0.4), and symptomatic treatment (p = 0.1041)) also have no significant influence on overall survival.

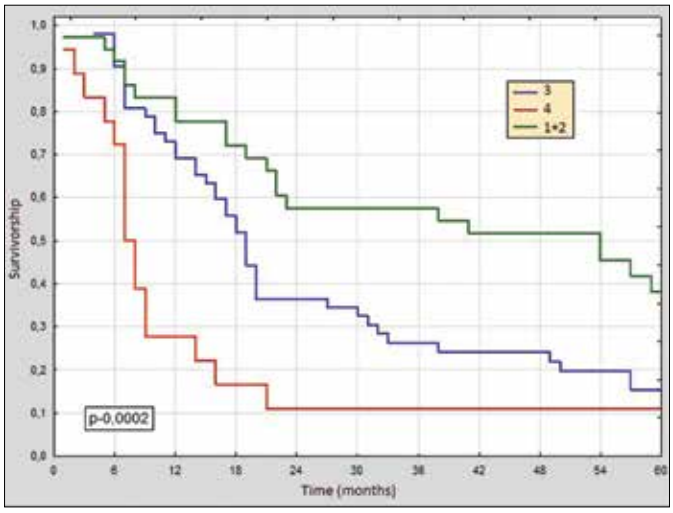

Figure 3. *Kaplan-Meier overall survivorship curves according to Fuhrman grade (p = 0.0002).*

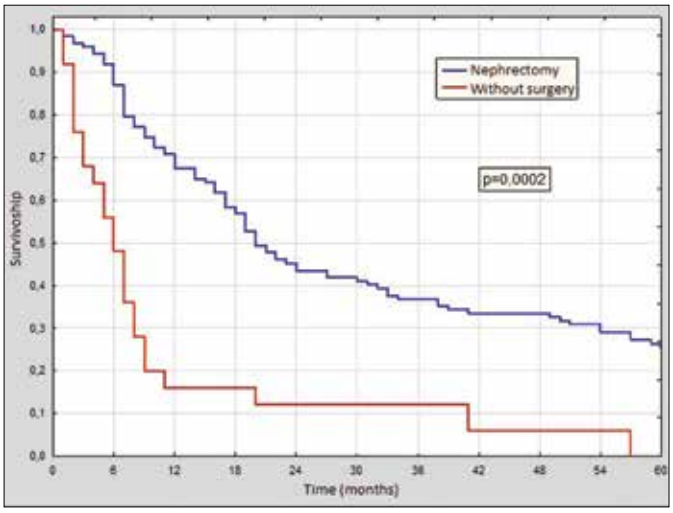

Figure 4. *Kaplan-Meier overall survivorship curves according to nephrectomy.*

Table 6. *Characteristics of continuous variables and univariate associations with survival*

Variable	n	(RR)	(CI)	p value
Age	145	1.007	0.991–1.023	0.4127
Tumor size on CT scans	102	1.013	1.005–1.021	0.0011
Hb	104	0.883	0.810–0.962	0.0046
RBC	93	0.935	0.728–1.200	0.5982
AP	63	1.001	0.999–1.004	0.3212
Serum urea	81	1.031	0.957–1.111	0.4196
Serum creatinine	80	0.997	0.989–1.003	0.3665
WBC	12	1.002	0.997–1.007	0.4473
LD	36	0.999	0.997–1.001	0.3956
GGT	40	1.002	1.000–1.004	0.0188
PLT	15	1.002	0.999–1.006	0.1226
Lung metasatsis size	25	0.992	0.971–1.012	0.4294
Liver metasatsis size	15	0.998	0.971–1.026	0.9095
Bone metasatsis size	9	0.985	0.963–1.008	0.2016
Lymph nodes metasatsis size	15	1.003	0.981–1.025	0.8171
Karnofsky PS	141	0.711	0.611–0.828	<0.005

Multivariate Cox regression analysis

The group of clinical, histopathological and biochemical data mentioned above were analyzed using multivariate Cox regression model with the aim of distinguishing independent factors of the overall survival prediction in a given population of patients with renal cancer. This analysis showed independent prognostic value of each particular factor in overall survival assessment and their usefulness. In the univariate analysis performance status expressed in Karnofsky scale and gammaglutamylotranspeptidase activity (GGTP) also appeared to have prognostic value; providing, however, that other variables were constant (Table 6).

Multivariate Cox model analysis revealed that several previously described factors had a statistically significant, independent influence on overall survival. The set of identified independent prognostic factors (IPFs) of overall survival (at $p < 0.05$) consisted of performance status, smoking history, hemoglobin concentration, AJCC anatomical staging, tumor grade, and presence of microvascular invasion. Presented data confirmed substantially longer survival rates of patients after surgery and indicated that nephrectomy is also an independent prognostic factor ($p < 0.02$) (Table 7).

DISCUSSION

Performance status (PS) had the strongest influence on OS in our case series, HR in group of patients with 2 and with 4 or 5 points of ECOG score was 2.78 and 14.92, respectively. This indexed measure of patient's general health was primarily devised to help oncologists qualify patents to systemic treatment with respect to their ability to withstand its adverse effects. It was included in RCC prognostication for the first time by Elson in 1988. He used PS (expressed in ECOG scale) as an IPF of OS in metastatic patients who underwent chemotherapy [17]. In RCC prognostication, PS played a greater role as prognostic factor of OS in patients with metastaic disease, especially qualified to various immune or targeted therapies (majority of scoring systems predicting outcomes in these groups of patients included PS in their sets of IPFs (Motzer, Lebovich, Denskov, Manola, etc.) [9, 15, 18, 19] Among major prognostic tools designed for the general population of patients with RCC, only Zisman's model focused on OS and identified PS as a prognostically useful variable [20, 21].

In the epidemiology of renal cancer, smoking is a well–documented risk factor of morbidity [22]. It is also an IPF of CCS in several other cancers, i.e. colon, bladder [23, 24]. However, information regarding its influence on survival in RCC is poor. Recently, researchers from UCLA published an extensive work describing the negative impact of smoking on clinicopathological features and survival outcomes in an investigated group of 802 patients with RCC [25]. There was a significant difference in distribution of adverse clinicopathological features (ECOG PS, severity of comorbidities, tumor extent, vascular invasion) with higher incidence in the smoking group. The analysis also showed the correlation between smoking history and frequency of p53 suppressor gene mutation, and confirmed p53 overexpression to be IPF of CCS in all patients. Multivariate analysis revealed smoking history to be IPF, both of CCS and OS in localized RCC, however, these results were not confirmed in the group of patients with metastatic disease. In our study, smoking history was an IPF of OS with HR ratio 3.27.

Serum hemoglobin was also found be an IPF of OS in our group. Anemia is a common finding in patients with cancer disease. In 2001 Caro et al. published a systemic quantitative review of 60 studies describing the role of anemia in various types of neoplasms [26]. In this review about 33% of patients were anemic and their median survival was decreased by 20–43%. Statistical analysis revealed a low hemoglobin level to be a negative predictor of OS, and the highest HRs were observed in cases of multiple myeloma and lymphoma (4.47 and 3.74, respectively). In anemic patients with RCC, HR was 1.9. The authors also highlighted controversies about the hemoglobin

Table 7. *Characteristics of independent prognostic factors identified in multivariate Cox regression analysis*

Characteristic	n	RR	95% CI	p
Cigarettes smoking				
no	103	1.000	–	–
yes	45	3.275	2.101–4.946	0.0000
ECOG Performance status				
0+1	96	1.000	–	–
2	23	2.781	1.583–4.884	0.0004
3+4	9	14.972	5.781–38.775	0.0000
Haemoglobin concentration (continuous variable in g/l)	114	0.888	0.804–0.980	0.0185
Tumor diameter (continuous variable in cm)	102	1.012	1.004–1.021	0.0054
AJCC anatomic stage				
I+II	37	1.000	–	–
III	20	2.109	1.064–4.183	0.0326
IV	74	3.286	1.878–5.750	0.0000
Fuhrman grade				
1+2	36	1.000	–	–
3	52	1.762	1.059–2.934	0.0293
4	18	3.023	1.519–6.016	0.0016
Microvascular invasion (MVI)				
No	105	1.000	–	–
Yes	43	1.628	1.049–2.525	0.0296
Nephrectomy				
No	25	1.932	1.100–3.394	0.0220
Yes	123	1.000	–	–

level cut–off value, which ranged from 8.5 g/dl to 14 g/dl, and the unclear link between anemia and tumor progression (apart from malignancies affecting bone marrow and other reticuloendothelial sites). In renal cancer, anemia is considered to result from elevated levels of inflammatory cytokines and increased catabolism induced by the tumor. However, in metastatic patients it may also be caused by systemic therapies administered to them. Some prognostic models stratifying risk in metastatic patients qualified to immune or targeted therapies use a low hemoglobin level as a negative predictor (Motzer, Negrier, Manola) [19, 27, 28].

In renal cancer, as well as in most of neoplasms, tumor involvement is the basic and most crucial prognostic factor predicting the course of disease. The first formal scale assessing the anatomical advancement of renal cancer correlating with OS was proposed by Robson. In 1978, however, it was replaced by the TNM classification involving consensus of US experts associated with the Union Against Cancer and the American Joint Committee. AJCC anatomic stages categorize patients with particular constellations of TNM features in respect to substantial interferences with distant outcomes, which can also vary depending on clinical situation [2, 29]. For instance, 5–year cancer–specific survival in patients who underwent surgical procedure range from 90–95% for stage I, 75–85% for stage II, 60–70% for stage III, and 20–30% for stage IV [30, 31]. Overall survival regardless of intervention, estimated in over 3,700,000 cancer cases was recorded in the National Cancer Data Base (NCDB) as 84.7%, 82.9%, 59.8%, and 11.1% for 1st, 2nd, 3rd, and 4th stages, respectively (Analysis from year 2000) [32, 33]. These data show that the presence of systemic metastases results in the highest reduction in survival rates. Nodal involvement is also associated with substantial decrease in survival. Surgical treatment significantly increases overall survival regardless of disease advancement. These finding correspond with our results.

Tumor grade, next to TNM, is an approved independent prognostic factor included in several major nomograms (Frank, Karakiewicz, Zissmann) [16, 20, 31, 34]. Similar results were observed in our group. Another histological finding affecting RCC prognosis is presence of microvascular invasion. Klatte et al., analyzing cancer specific survival in 258 patients with papillary renal cancer confirmed the usefulness of this prognostic factor, and the nomogram he proposed is one of the highest prediction accuracy (94%) [35]. In our work, 2–and 5–year patients' overall survival, in dependence to the presence of MVI, was

45% and 25% (p <0.05), respectively. While congruent results were reported by Lang and co–authors (71% and 62% respectively) [36].

CONCLUSIONS

Data regarding RCC prognostication in Polish literature are extremely poor. There are only a few Polish studies assessing RCC prognostic factors by the use of modern statistical tools like multivariate Cox regression analysis. The prognostic value of clinical variables (expressed as HR) varies in different studies even when they applied to similar group of patients. Their role is well established for some, but for others (hemoglobin concentration, smoking history) is still debatable. Smoking history seems to be new IPF with strong negative impact on survival in patients with RCC.

Present reviews of major scoring systems emphasize the difference of their discriminating ability in different populations. For instance, discriminating ability of postoperative nomogram designed by Karakiewicz for all stages RCC in external validation performed on Canadian and North American populations ranged between 84 and 88%. Yet, when tested on British population its value was 74% [3, 37].
None of the scoring systems have been validated for the Polish population. Polish clinicians just have to assume that foreign prognostic models are applicable to assess outcomes in their patients. This lack of certainty, apart from doubts in their additional value, is one of reasons discouraging clinicians from using scoring systems in RCC prognostication in Poland. We believe that Polish population deserves adequate validations of modern prognostic models and evaluation of IPFs of RCC progression.

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