Correlation Among Clinical and Pathological Parameters and Disease-Free Survival of Patients with Renal Cancer Treated with Surgery at a Public Cancer Clinic in Curitiba

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Correlação entre os Parâmetros Clínicos, Patológicos e a Sobrevida Livre de Doença de Pacientes com Câncer Renal Tratados com Cirurgia em um Centro Oncológico do Sistema Público de Curitiba

Correlación entre Parámetros Clínicos, Patológicos y Supervivência Libre de Enfermedad de Pacientes con Cáncer Renal Tratados con Cirugía en un Centro Oncológico Público de Curitiba

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ABSTRACT

Introduction: Kidney cancer corresponds to the 13th most incident cancer in the world, and the third most common type of genitourinary cancer. Most patients are asymptomatic, and the diagnosis used to be incidental during routine imaging exams. Surgical treatment is the gold standard. **Objective:** To correlate clinical and pathological parameters with disease-free survival in renal cancer patients submitted to nephrectomy. **Method:** Retrospective study with 99 patients who underwent surgical treatment of kidney cancer from 2010 to 2020. Clinical and pathological parameters were compared with the clinical oncologic outcome after surgery. **Results:** Ninety-nine patients were followed-up postoperatively for an average time of 26.9 months, and the mean disease-free survival was 61.9%. Univariate analysis showed that tumor size >7 cm and Fuhrman grades III and IV were risk factors related to disease progression after nephrectomy (p=0.046 and CI=1.017-7.083; p=0.005 and CI=1.725-23.004, respectively). In the multivariate analysis, tumor size > 7cm (p=0.014 and CI=1.290-9.326) and Fuhrman grades III and IV (p=0.028 and CI=1.174-16.616) were identified as predictors of progression. **Conclusion:** Tumor size >7 cm and/or Fuhrman grades III or IV are risk factors for tumor recurrence after surgical treatment of renal cancer.
Key words: kidney neoplasms; survival analysis; nephrectomy.

RESUMO

Introdução: O câncer renal corresponde a 13ª neoplasia mais incidente no mundo, sendo o terceiro tipo de câncer geniturinário mais comum. A maioria dos pacientes é assintomática, ocorrendo o diagnóstico de maneira incidental durante a realização de exames de imagem. O tratamento padrão-ouro é o cirúrgico. **Objetivo:** Correlacionar os parâmetros clínicos e patológicos com a sobrevida livre de doença em pacientes com câncer renal submetidos à nefrectomia. **Método:** Estudo retrospectivo com 99 pacientes submetidos a tratamento cirúrgico do câncer renal no período de 2010 a 2020. Foram comparados os parâmetros clínicos e patológicos com o desfecho clínico oncológico após nefrectomia. **Resultados:** Os 99 pacientes tiveram seguimento pós-operatório médio de 26,9 meses, sendo a sobrevida livre de doença (média) de 61,9%. A análise univariada demonstrou que as variáveis tamanho de tumor >7 cm e graus de Fuhrman III e IV estiveram relacionadas à progressão de doença após a nefrectomia (p=0,046 e IC=1,017-7,083; p=0,005 e IC=1,725-23,004, respectivamente). Na análise multivariada, o tamanho do tumor >7 cm (p=0,014 e IC=1,290-9,326) e os graus de Fuhrman III e IV (p=0,028 e IC=1,174-16,616) foram identificados como fatores preditores à progressão. **Conclusão:** O tamanho tumoral >7 cm e/ou os graus III ou IV de Fuhrman são fatores de risco para recorrência tumoral após o tratamento cirúrgico do câncer renal.
Palavras-chave: neoplasias renais; análise de sobrevida; nefrectomia.

RESUMEN

Introducción: El cáncer de riñón corresponde a la 13ª neoplasia más incidente en el mundo, siendo el tercer tipo de cáncer genitourinario más común. La mayoría de los pacientes son asintomáticos, realizándose el diagnóstico de forma incidental durante las pruebas de imagen. El tratamiento estándar de oro es el quirúrgico. **Objetivo:** Correlacionar parámetros clínicos y patológicos con la supervivencia libre de enfermedad en pacientes con cáncer renal sometidos a nefrectomía. **Método:** Estudio retrospectivo con 99 pacientes sometidos a tratamiento quirúrgico de cáncer renal desde 2010 hasta 2020. Se compararon los parámetros clínicos y patológicos con el resultado clínico oncológico tras la nefrectomía. **Resultados:** Los 99 pacientes tuvieron un seguimiento postoperatorio medio de 26,9 meses, siendo la supervivencia libre de enfermedad (mediana) de 61,9%. El análisis univariado demostró que las variables tamaño del tumor >7 cm y grados III y IV de Fuhrman fueron factores relacionados con la progresión de la enfermedad tras la nefrectomía (p=0,046 e IC=1,017-7,083; p=0,005 e IC=1,725-23,004, respectivamente). En el análisis multivariante, el tamaño del tumor >7 cm (p=0,014 e IC=1,290-9,326) y grados de Fuhrman III y IV (p=0,028 e IC=1,174-16,616) fueron identificados como predictores de progresión. **Conclusión:** El tamaño tumoral >7 cm y/o los grados III o IV de Fuhrman son factores de riesgo para la recidiva tumoral tras el tratamiento quirúrgico del cáncer renal.
Palabras clave: neoplasias renales; análisis de supervivencia; nefrectomía.

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INTRODUCTION

Renal cell carcinoma (RCC) is the 13th most common neoplasm in the world, affecting older adults mostly, accounting for 3% of all cancers and greater incidence in Western countries[1]. Approximately 200 thousand new renal cancer cases are diagnosed annually in the world[2].

The incidence of RCC is increasing from 2.3% to 4.3% each year in the last three decades in the United States of America (USA). One of three patients diagnosed will die as a result of the progression of the disease to metastasis[3].

Most of the patients are asymptomatic[4] and 75% of the cases are diagnosed incidentally during routine exams (ultrasound, computed tomography or magnetic resonance).

TNM staging recommended for clinical and scientific purposes classifies the extension of the disease, based in imaging exams which reveal whether it affected the kidney alone or spread to other structures, if regional lymph nodes and/or remote metastases are found, requiring continuous reclassification[5,6]. The cases are diagnosed mostly as small renal mass smaller than 4 cm and better prognosis post curative surgical treatment[7].

The gold standard treatment for localized renal cancer is nephrectomy without evidence if other treatments are more effective to control the disease and the outcome mortality[8].

Currently, partial nephrectomy is gaining more space in the world scenario as it causes less intra and postoperative morbidity shown in a Mayo Clinic[9] study where patients submitted to total nephrectomy compared to those submitted to partial nephrectomy needed more blood transfusion (32.7% *versus* 7.8%; p=0.0001), more incidence of medical complications (20.4% *versus* 9.4%; p=0.0001), high length of stay (9.8% *versus* 7.6%; p=0.0001) and increase of postoperative serum creatinine (87.9% *versus* 55.6% p=0.0001)[9]. However, for tumors larger than 7 cm and/or anatomically unfavorable, radical nephrectomy is indicated[1]. After curative surgical treatment, patients should be followed up with imaging exams to detect possible tumor recurrence[10].

One of the hypothesis is that patients consulted at Brazilian public institutions due to possible delays of access, have the diagnostic and treatment of renal tumors greater or more aggressive, which can reduce the chances of cure. A study conducted by "*Hospital Sírio Libanês*" and by "*Hospital das Clínicas*" of *São Paulo* suggested that the socioeconomic status of the patient is a factor for dismal prognosis[11].

The objective of this article is to correlate the clinical parameters (sex, symptoms at the diagnosis and size of the tumor) and pathological (pathologic type, Fuhrman grade, pathological staging, lymph nodes and angiolymphatic invasion) with progression-free oncological survival in patients with RCC submitted to surgical treatment at the oncology service of '*Hospital São Vicente*" from 2010 to 2020.

METHOD

Observational, retrospective study with data collected from electronic charts of patients submitted to total or partial nephrectomy to treat RCC in a single hospital from January to December 2020. The Institutional Review Board (IRB) of the institution approved the study, report 4,034,225 (CAAE (submission for ethical review): 31348920.3.0000.0020).

The initial sample consisted in 166 patients submitted to nephrectomy during the period investigated. According to the exclusion criteria, 67 patients were not enrolled due to incomplete charts, cytoreductive nephrectomy, absence of histological malignancy, death while the study was being conducted. Eventually, 99 patients remained in the final sample.

The variables evaluated were: clinical parameters (sex, race, comorbidities – systemic arterial hypertension, diabetes, dyslipidemia), tobacco use, symptoms as back pain, hematuria, weight loss, serum creatinine before and after the surgery. The pathological parameters evaluated were: TNM staging, Fuhrman histological grade, histological type of the primary tumor, location, dimension of the tumor, angiolymphatic invasion and compromised lymph nodes. Clinical and pathological data were correlated with the presence or absence of recurrence during follow-up. Oncologic cure was defined when the patient did not relapse, or the disease progressed during the oncological follow-up at the institution.

For each one of the variables, the null hypothesis of no association between the variable and relapse (progression or non-progression) was tested *versus* the alternative hypothesis that the association existed. The quantitative variables were described by mean and minimum and maximum standard deviation. For categorical variables, frequency and percent were calculated. Progression-free time was described by Kaplan-Meier curves. For factors associated with time of progression, Cox regression models were adjusted. Wald test was utilized to evaluate the significance of the variables and hazard ratio (HR) as measure of association estimated with confidence intervals of 95%. Values of $p<0.05$ indicated statistical significance. The software Stata version 14.1. of StataCorpLP, USA was utilized to analyze the data.

RESULTS

Of the initial 166 patients screened, 67 were excluded due to incomplete charts, cytoreductive surgeries, absence of histological malignancy or death while the study was being conducted. The 99 patients who have submitted to partial or radical nephrectomy were enrolled (final n of the study).

Ninety-nine patients were investigated with mean age of 59 years old; 50.5% of the patients were males, and 92.8% were Caucasian. Systemic arterial hypertension was found in 64.4% of the patients, 24,4% had diabetes, 34.1%, dyslipidemia, 26.7% smoked, 46.2% were symptomatic, of which 29.7% had back pain, 29.7%, hematuria and 6.6%, weight loss. Preoperative creatinine was 1.2 mg/dL and postoperative, 1,3 mg/dL related to renal function; during follow-up, the last measure was 1.2 mg/dL; glomerular filtration rate at the last follow up visit was 62.9 mL/min/1.73m^2 (Table 1).

Clear cell renal carcinoma was the predominant histological type accounting for 90.1%, the chromophobe renal cell carcinoma, 4.3% and papillary renal carcinoma, 3.2% and the eosinophilic renal carcinoma and adenocarcinoma with 1.1% each. Fuhrman I was found in 18% of the patients, Fuhrman II, 28%, Fuhrman III, 42% and Fuhrman IV, 10%. The tumors size were grouped in three groups: <4 cm (14.4%), 4-7 cm (44.4%) and >7 cm (41.1%). Partial nephrectomy was performed in 16.2% of the cases *versus* radical nephrectomy in 83.8% (Table 1).

The recurrence-free survival was 77.8% with mean follow-up of 26.9 months; the mean follow-up of progression-free patients was 29 months *versus* 19.8 months for those who progressed. Twenty-two patients progressed with mean time of recurrence of 19.8±16.0 months. Local progression was single or multiple: 40% only at the lung, 10% only at bones, 10% only at lung associated with lymph nodes and 5% at lymph nodes alone. Of the 22 patients, only four did not submit to any post-progression therapy. The other 16 were treated only with immune therapy (33.3%), inhibitors of angiogenesis (25%), chemotherapy (16.7%), immune therapy associated with inhibitors of angiogenesis (16.7%), or immune therapy associated with chemotherapy (8.3%) as shown in Table 2.

The percent of progression-free cases according to time of follow-up was presented according to Kaplan-Meier estimator (estimates and plots survival function from several lifetime data): day 0 (surgery) = 100% progression-free; 1 month = 99%; 3 months = 97.9%; 6 months = 91.2%; 12 months = 88.5%; 18 months = 87.1%; 24 months = 85.3%; 36 months = 74.4%; 48 months = 64.7%; 60, 80 and 94 months = 61.9%[12] (Graph 1).

Only the variables "grouped size of the tumor" and "grouped Fuhrman" of the univariate analysis were relevant: grouped size of the tumor >7 cm (p=0.046; HR 2.683; CI=1.017-7.083) and grouped Fuhrman grades III and IV (p=0.005; HR 6.298; CI=1.725-23.004) as shown in Table 3.

To evaluate in conjunction the factors associated with progression-free time, a Cox model was adjusted including the explanatory variables: tumor size (≤7 or >7 mm); Fuhrman histologic grade (1-2 or 3-4) and back pain. These variables presented p<0.10 in the univariate analysis. For each one of the variables in the presence of the other, the null hypothesis that there was no association between the variable and progression-free time (time until progression) *versus* the alternative hypothesis that there was association.

Only the grouped Fuhrman grades III and IV had statistical significance (p=0.028; HR 4.417) in the analysis of the criteria presence of back pain (p=0.014; HR 3.468), tumor size >7 cm (p=0.015; HR 3.192) and Fuhrman grade in the multivariate analysis (Table 4).

DISCUSSION

The study showed the evolution of the patients submitted to nephrectomy at a Brazilian public service. With mean follow-up of 26.9 months, most of the patients (77.8%) were disease-free, but 22.2% relapsed and/or had oncologic progression. The elevated progression rate can be justified by late diagnosis for the patients consulted by the National Health System (SUS).

Approximately 72% and 42% of the patients were diagnosed at stage pT1 at *Hospital Sírio Libanês* (private) and at *Hospital das Clínicas de São Paulo* (public) respectively, corroborating the aforementioned study conducted by both institutions, based in the hypothesis that socioeconomic status is an independent factor of progression, even if the incidence of RCC was not directly investigated. As the likelihood of progression of RCC for pT1 tumors is quite low compared with other stages, a higher progression rate at public hospitals is more often found than in private hospitals[11].

The tumor size >7 cm (grouped) and Fuhrman (grouped) were statistically significant in the analysis of epidemiologic, clinic and laboratory factors of disease-free survival. Of the patients with tumor size >7 cm, 35.1% had disease progression, while for tumor size 4-7 cm, only 15% progressed, which reinforces the theory found in the literature that the tumor size at diagnosis is an important risk factor for disease progression[13]. Only 14.4% of the patients were diagnosed with tumors < 4 cm in the present study in counterpart to the literature where 64% of the

Table 1. Demographic and clinical profile of patients with renal cancer submitted to curative nephrectomy and surgery-related histopathological variables

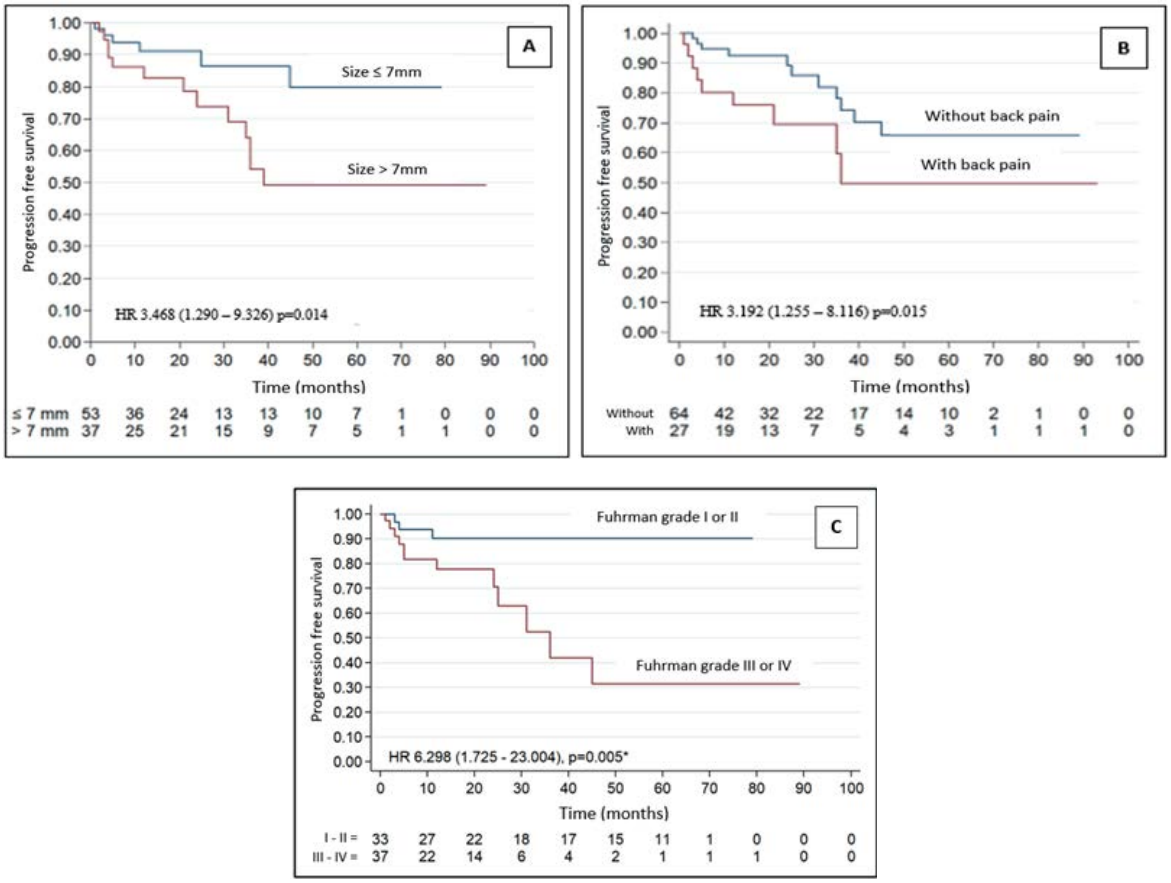
Variable	n	Classification	Results*
Age at surgery (years)	99		59.4±11.1 (31-86)
Sex	99	Female	49 (49.5%)
		Male	50 (50.5%)
Race	97	White	89 (92.8%)
		Black	5 (5.2%)
		Brown	3 (3.1%)
Arterial hypertension	90	No	32 (35.6%)
		Yes	58 (64.4%)
Diabetes	90	No	68 (75.6%)
		Yes	22 (24.4%)
Dyslipidemia	88	No	58 (65.9%)
		Yes	30 (34.1%)
Tobacco use	90	No	66 (73.3%)
		Yes	24 (26.7%)
Symptomatic	91	No	49 (53.8%)
		Yes	42 (46.2%)
Back pain	91	No	64 (70.3%)
		Yes	27 (29.7%)
Hematuria	91	No	64 (70.3%)
		Yes	27 (29.7%)
Weight loss	91	No	85 (93.4%)
		Yes	6 (6.6%)
Preoperative Cr	82		1.2±0.4 (0.5-2.6)
Postoperative Cr	86		1.3±0.4 (0.6-3.6)
Last Cr	84		1.2± 0.4 (0.7-3.6)
Delta Cr	76		0.1±0.4 (-1.2-1.3)
GFR	84		62.6±19.6 (18-129)
Primary tumor	91	1= clear cells renal carcinoma	82 (90.1%)
		2= chromophobe renal cell carcinoma	4 (4.3%)
		3= papillary renal cell carcinoma	3 (3.2%)
		4= eosinophilic renal cell carcinoma	1 (1.1%)
		5= adenocarcinoma	1 (1.1%)
Fuhrman	70	Grade 1	13 (18.6%)
		Grade 2	20 (28.6%)
		Grade 3	30 (42.9%)
		Grade 4	7 (10%)
Fuhrman (dichotomized)	70	Grade 1 or 2	33 (47.1%)
		Grade 3 or 4	37 (52.9%)
Angiolymphatic invasion	99	No	82 (82.8%)
		Yes	17 (17.2%)
Size (cm)	90	<4	13 (14.4%)
		4-7	40 (44.4%)
		>7	37 (41.1%)
Procedure	99	Radical	83 (83.8%)
		Partial	16 (16.2%)

Captions: Cr = Creatinine; GFR = glomerular filtration rate.
(*) Described by mean ± standard-deviation (minimum-maximum) – quantitative variables – or by frequency (percent) – categorical variables.

Table 2. Oncologic progression, metastasis location, systemic treatments and time of follow-up

Variable	n	Classification	Results*
Oncologic progression	99	No	77 (77.8%)
		Yes	22 (2.,2%)
Site of metastasis and progression	20	1: Lung	8 (40%)
		2: Bones	2 (10%)
		3: Lung + lymph nodes	2 (10%)
		4: Mesentery	2 (10%)
		5: Liver	1 (5%)
		6: Local + pancreas	1 (5%)
		7: Lymph nodes	1 (5%)
		8: Lung + CNS	1 (5%)
		9: Lung + liver	1 (5%)
		10: Lung + bones	1 (5%)
Other treatments	16	1: Immune therapy	4 (33.3%)
		2: Inhibitor of angiogenesis	3 (25%)
		3: Chemotherapy	2 (16.7%)
		4: Immune therapy + inhibitor of angiogenesis	2 (16.7%)
		5: Immune therapy + chemotherapy	1 (8.3%)
Follow up (months)	99	All	26.9±23.4 (1-93)
	77	Without progression	29±24.8 (1-93)
	22	With progression	19.8±16.0 (1-48)

Caption: CNS = Central Nervous System.
(*) Described by mean ± standard-deviation (minimum-maximum) – quantitative variables – or by frequency (percent) – categorical variables.



Graph 1. Kaplan-Meier estimates for the proportion of progression-free cases with variables tumor size (A), back pain (B) and Fuhrman grade (C)

Table 3. Disease survival-free univariate analysis of epidemiologic, clinic, laboratory, histopathologic and surgical factors

Variable	Classification	n	% progression	p*	HR (CI95%)
Age at surgery (years)	(mean ± standard deviation)	77 22	No: 60.1±11 Yes: 57±11.2	0.524	0.988 (0.951-1.026)
Preoperative Cr	(mean ± standard deviation)	62 20	No: 1.16±0.43 Yes: 1.17±0.51	0.432	0.656 (0.229-1.876)
Postoperative Cr	(mean ± standard deviation)	66 20	No: 1.31±0.44 Yes: 1.29±0.47	0.817	0.877 (0.287-2.674)
Last Cr	(mean ± standard deviation)	64 20	No: 1.23±0.42 Yes: 1.26±0.32	0.934	1.060 (0.270-4.165)
Delta Cr	(mean ± standard deviation)	56 20	No: 0.08±0.45 Yes: 0.07±0.42	0.502	1.424 (0.507-4.005)
GFR	(mean ± standard deviation)	64 20	No: 62.3±20.2 Yes: 63.6±17.8	0.621	1.006 (0.988-1.029)
Sex	Female Male	49 50	10 (20.4%) 12 (24.0%)	0.534	1.305 (0.563-3.025)
Arterial Hypertension	No Yes	32 58	9 (28.1%) 11 (19%)	0.687	0.834 (0.344-2.022)
Diabetes	No Yes	68 22	15 (22.1%) 5 (22.7%)	0.660	1.257 (0.454-3.482)
Dyslipidemia	No Yes	58 30	15 (25.9%) 6 (16.7%)	0.454	0.678 (0.245-1.874)
Tobacco use	No Yes	66 24	16 (24.2%) 4 (16.7%)	0.979	0.985 (0.324-2.995)
Symptomatic	No Yes	49 42	8 (16.3%) 12 (28.6%)	0.349	1.534 (0.626-3.758)
Back pain	No Yes	64 27	11 (17.2%) 9 (33.3%)	0.067	2.280 (0.942-5.518)
Hematuria	No Yes	74 17	13 (17.6%) 7 (41.2%)	0.185	1.865 (0.742-4.687)
Weight loss	No Yes	85 6	17 (20%) 3 (50%)	0.204	2.220 (0.649-7.593)
Size (cm)	<4 4-7 >7	13 40 37	0 (0%) 6 (15%) 13 (35.1%)	-	-
Size (grouped)	≤7 (ref.) >7	53 42	6 (11.3%) 18 (42.9%)	0.046	2.683 (1.017-7.083)
Procedure	Radical (ref.) Partial	83 16	20 (24.1%) 2 (12.5%)	0.343	0.495 (0.116-2.121)
Fuhrman	Grade I Grade II Grade III Grade IV	13 20 30 7	0 (0%) 3 (15%) 6 (20%) 6 (85.7%)	-	-
Fuhrman (grouped)	Grades I-II (ref.) Grades III-IV	33 37	3 (9.1%) 12 (32.4%)	0.005	6.298 (1.725-23.004)

Captions: HR = hazard ratio; CI 95% = confidence interval 95%; Cr = creatinine; GFR = glomerular filtration rate; ref. = classification of reference of analysis.
(*) Significance of the Wald test of the Cox univariate regression model.

Table 4. Multivariate analysis of progression-free time with independent variables: size of the tumor and back pain; size of the tumor, back pain and Fuhrman grade

Variable	Classification	N valid	p*	HR (CI 95%)
Size	≤7 (ref.) >7	Progression: 15[a] Censored: 51[b] n in the model: 66[c]	0.115	2.447 (0.805-7.442)
Back pain	No (ref.) Yes		0.071	2.768 (0.917-8.359)
Fuhrman (grouped)	Grades I-II (ref.) Grades III-IV		0.028	4.417 (1.174-16.616)

Captions: HR = hazard ratio; CI 95% = confidence interval of 95%; ref. = classification of reference of analysis.
(a) Number of cases with disease progression during follow-up.
(b) Number of disease-free cases during follow-up.
(c) Total number of cases included in the multivariate analysis without missing data of the variables included in the model: disease-free survival in months; progression; size (grouped); back pain and Fuhrman (grouped).
(*) Significance of Wald test, p<0.05.

tumors were smaller than 4 cm[14], once again strengthening the hypothesis that patients are being diagnosed later.

Back pain at diagnosis was reported by 27% of the patients investigated herein and 33% had disease progression (p=0.067). Future studies are expected to address more thoroughly the topic "back pain in patients with renal carcinoma" considering the subjectivity of this complaint and possibility of several etiologic factors.

The present study concluded that 52.9% of the patients presented Fuhrman grades III or IV, equivalent to risk factor for disease progression. Of the patients with grade III, 20% progressed, and with grade IV, 85.7% progressed. These data are consistent with the literature as Fuhrman grade is an important factor of relapse and disease progression and strong independent predictor of suvival[15].

The evolution of the patients submitted to nephrectomy at a public Brazilian cancer service was described. The interpretation of the results may help to develop strategies to reduce the impact of renal cell carcinoma and post-treatment repercussions considering that the data are referred to a public institution, main source of medical care for most part of the Brazilian population.

The limitations of the study are the retrospective design with review of electronic charts with heterogeneous data collected and one single cancer center, an obstacle for the generalization of the results.

CONCLUSION

Tumor size > 7 cm and histological Fuhrman grade III or IV are predictors of disease progression post-surgery treatment of RCC for the population consulted at a public uro-oncological center of Curitiba (Paraná). Although no screening RCC is indicated, early diagnosis of small size tumors may lead to better prognosis.

CONTRIBUTIONS

All the authors contributed substantially to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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