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Effect of Symptom Graduation on Oncologic Outcomes in Patients with Renal Cell Carcinoma and Hematuria

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MFDO and JRJC designed the study. Author ENI wrote the protocol, and wrote the first draft of the manuscript. Authors EPM and GBG managed the literature searches and analyses of the study performed. Authors ENI and EPM were responsible for the final version of this manuscript. Authors WCN and MS were responsible for critical revision. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Symptoms associated with renal cell carcinoma characterize high-risk disease. Hematuria is the most common symptom and usually occurs as a result of urothelial invasion. The objective of this study was to evaluate the prognostic value of progressive symptomatic disease in patients with kidney cancer.
Place and Duration of Study: Sao Paulo Cancer Institute at University of Sao Paulo School of Medicine between 2005 and 2009.
Methodology: Data was prospectively recorded at our database and retrospectively reviewed. Sixty-six individuals who presented with macroscopic hematuria were included in our analysis.

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Patients were divided into three groups: (1) Exclusive hematuria (27 patients), (2) Hematuria associated with another symptom (23 patients), and (3) Hematuria associated with two or more symptoms. We evaluated these groups for histopathology, kidney function, recurrence, and survival characteristics.
Results: Mean tumor diameter was 8.5 cm, 11 cm and 13.4 cm for groups (1), (2) and (3). Recurrence-free survival was 89%, 91%, and 69% and overall survival was 96%, 79%, and 56% for groups (1), (2) and (3), respectively. The mean follow-up time was 97.6 months and the disease-free survival rate was 84.8%. Cox regression analysis showed a death risk 10.5 times higher in group (3) when compared to Group (1).
Conclusion: Association of two or more symptoms with hematuria impairs prognosis of patients surgically treated for kidney cancer.

Keywords: Hematuria; renal cell carcinoma; prognosis; urinary tract cancer.

ABBREVIATIONS

ANOVA : Analysis of Variance
MDRD : Modification of Diet in Renal Disease
RCC : Renal Cell Carcinoma
SD : Standard Deviation

1. INTRODUCTION

Global mortality by renal cell carcinoma (RCC) has increased in the last two decades, but fortunately, not as significant as the increase of its incidence. There are estimates that approximately 3.8 billion dollars were spent in the U.S.A. in 2010 for treating RCC [1].

Classically, a significant number of kidney tumors are detected due to the presence of the classical triad: hematuria, flank pain, and palpable mass. Although such triad is currently rare, around 20% to 40% of those patients present with locally advanced or metastatic disease upon diagnosis [2].

Nowadays, 15% to 47% of the RCC are found incidentally [3-5]. In these cases lower clinical stage are found in comparison to symptomatic lesions. Subsequently, such lesions, which are both clinically and physiologically less aggressive, lead to better survival and recurrence outcomes when compared to symptomatic tumors [6].

The relation between initial onset, clinical characteristics, and evolution has been the focus of several papers, many of which state that lesions found incidentally and symptomatic tumors are markedly distinct regarding size, degree of vascular invasion and survival [7-9]. The size of the tumor upon presentation may influence the performance-status relation, which has clear a correlation with the survival rate [9]. In addition to TNM staging, the prognosis of RCC is, however, influenced by many anatomic and pathological features, such as tumor size, histological type, Fuhrman nuclear grading, microvascular invasion, and lymph node involvement [10,11].

In symptomatic patients, macroscopic isolated hematuria has emerged as the most common initial symptomatic clinical presentation. The objective of this study is to evaluate clinical-pathological findings in patients with kidney cancer patients presenting with macroscopic hematuria and to determine the implications in prognosis regarding oncological outcomes, survival and renal function.

2. MATERIALS AND METHODS

Clinical data of patients surgically treated due to malignant renal neoplasms between June 2005 and December 2009 were obtained retrospectively from electronic records system and from the prospectively fed databank which is maintained by the Urology & Oncology Sector of our institution. Patients were divided in three groups: 1) Exclusive hematuria, 2) Hematuria associated to another symptom, and 3) Hematuria associated to two or more symptoms. Pain and anorexia reported by patients were considered symptoms related to RCC. Weight loss was considered significant when a decrease in corporal weight higher of 10% in a 6-month period was confirmed. Palpable mass was also considered a symptom related to RCC either by patient self report or through physical examination. The following parameters were evaluated: age, gender and clinical presentation. After pathological analysis lesions were classified according to tumor size, nuclear Fuhrman grading, histological type, presence of microvascular invasion, presence of tumor necrosis, kidney capsule invasion, lymph node

invasion, perirenal fatty tissue invasion and adrenal gland invasion.

During follow-up, patients returned at our outpatient clinic every four months during the first year, and subsequently, at six-month intervals. Anamnesis and clinical examination was performed routinely. Blood chemistry tests and radiological (chest and abdomen CT) exams were requested when necessary upon physician decision.

Patient evolution curves were defined based on information such as presence of recurrence of disease and need of treatment. Recurrence was confirmed with biopsy in most cases, unless unequivocal diagnosis of metastatic disease was established. Systemic recurrence and survival rate were evaluated by actuarial curves. Post-operative creatinine was determined as the value obtained during latest follow-up visit. Estimated glomerular filtration rate was determined using the MDRD equation.

Statistical analysis was performed using the Log Rank approach and Kaplan Meier curves, Chi-Squared test, ANOVA test and Kruskal-Wallis test Cox Regression. This study was approved by the Institutional Review Board under number 0178/10. The patients' informed consent was waived.

3. RESULTS

Sixty-six patients exhibited macroscopic hematuria as an initial clinical manifestation of kidney tumors and were selected for analysis. Group characteristics regarding age and other demographic data are described on Table 1.

Radical nephrectomy was not carried out in two patients of Group 2 because they had single kidneys. Clinical characteristics of renal neoplasms from different groups are presented in Table 2.

The quantitative and qualitative description of the signs and symptoms associated to hematuria are described in the Table 3.

After nephrectomy, surgical specimens were analyzed regarding histological types, which are described in Table 4. The distribution of different histological types within the three groups was not significant (P = 0.136).

The data present in Table 5 describe the pathological characteristics and pathologic stage of tumors. There was no significant difference regarding T stage between groups.

Table 1. Patients who presented macroscopic hematuria

Features	Group 1	Group 2	Group 3	Total
Number of patients	27 (41%)	23 (35%)	16 (24%)	66 (100%)
Age				
mean (SD)	58 (±15)	60 (±14)	57 (±10)	-
Gender				
Male	16 (59%)	14 (61%)	8 (50%)	38 (58%)
Female	11 (41%)	9 (39%)	8 (50%)	28 (42%)

Table 2. Tumoral features and proposed surgery

Features	Group 1	Group 2	Group 3	Total	*P*
Nephrectomy					
Radical	27 (100%)	22 (91.7%)	16 (100%)	65 (97%)	
Partial	0 (0%)	2 (8.3%)	0 (0%)	2 (3%)	
Laterality					
Right	17 (63%)	14 (58.3%)	5 (31.3%)	36 (53.7%)	0.151
Left	10 (37%)	9 (37.5%)	11 (68.7%)	30 (44.8%)	
Bilateral	0 (0%)	1 (4.2%)	0 (0%)	1 (1.5%)	
Tumor size					
< 4 cm	1 (3.7%)	0 (0%)	0 (0%)	1 (1.5%)	0.002
4 – 7cm	8 (29.6%)	4 (17.4%)	1 (6.3%)	13 (19.7%)	
> 7cm	16 (59.3%)	19 (82.6%)	14 (87.5%)	49 (74.3%)	
Indeterminate	2 (7.4%)	0 (0%)	1 (6.2%)	3 (4.5%)	
Mean (cm) (SD)	8.5 (±3.5)	11 (±4)	13.4 (±4.7)	-	

Table 3. Signs and symptoms associated to the hematuria

Features	Group 2 (N=23)	Group 3 (N=16)	Total
Associated sign or symptom			
Pain	19 (82.6)	15 (93.8)	34 (51.5)
Anorexia	1 (4.4)	1 (6.3)	2 (3)
Palpable mass	2 (8.7)	14 (87.5)	16 (24.2)
Weight loss	1 (4.3)	7 (43.8)	8 (12.1)

Table 4. Histological type of tumor

Features	Group 1	Group 2	Group 3	Total
Histology (%)				
Clear cells	15 (55.6)	17 (73.9)	13 (81.1)	45 (68.2)
Papillary	5 (18.5)	1 (4.4)	1 (6.3)	6 (11)
Chromophobe	1 (3.7)	2 (8.7)	1 (6.3)	4 (6.1)
Sarcomatoid differentiation	3 (11.1)	0 (0)	1 (6.3)	4 (6.1)
Medullar	1 (3.7)	0 (0)	0 (0)	1 (1.5)
Indeterminate	1 (3.7)	0 (0)	0 (0)	1 (1.5)

Table 5. Histological and pathological features and staging

Features	Group 1	Group 2	Group 3	Total	*P*
Invasion and necrosis					
Lymph node					0.115
Positive	3 (11.1%)	4 (17.4%)	6 (37.5%)	13 (19.7%)	
Negative	24 (88.9%)	19 (82.6%)	10 (62.5%)	53 (80.3%)	
Renal capsule invasion					
Positive	9 (33.3%)	12 (52.2%)	12 (75%)	33 (50%)	0.011
Negative	18 (66.7%)	11 (47.8%)	4 (25%)	33 (50%)	
Adrenal invasion	1 (3.7%)	2 (8.7%)	5 (31.3%)	8 (12.1%)	
Positive	1 (3.7%)	2 (8.7%)	5 (31.3%)	8 (12.1%)	0.014
Negative	26 (96.3%)	21 (91.3%)	11 (68.7%)	58 (87.9%)	
Microvascular invasion					
Positive	5 (18.5%)	6 (26.1%)	10 (62.5%)	21 (31.8%)	0.004
Negative	22 (81.5%)	17 (73.9%)	6 (37.5%)	45 (68.2%)	
Necrosis					
Present	15 (55.6%)	14 (60.9%)	15 (93.7%)	44 (66.7%)	0.008
Absent	12 (44.4%)	9 (39.1%)	1 (6.3%)	22 (33.3%)	
Perirenal fatty tissue					
Positive	8 (29.7%)	6 (26.1%)	9 (56.3%)	23 (34.8%)	0.125
Negative	19 (70.3%)	17 (73.9%)	7 (43.7%)	43 (65.2%)	
Fuhrman grade					
1	2 (7.4%)	4 (17.4%)	1 (6.3%)	7 (10.6%)	0.720
2	7 (26%)	6 (26.1%)	4 (25%)	17 (25.8%)	
3	8 (29.6%)	9 (39.1%)	7 (43.7%)	24 (36.4%)	
4	8 (29.6%)	3 (13%)	4 (25%)	15 (22.7%)	
Indeterminate	2 (7.4%)	1 (4.4%)	0	3 (4.5%)	
Staging (%)					
T1	5 (18.5%)	4 (17.4%)	0	9 (13.64%)	
T2	6 (22.3%)	6 (26%)	4 (25%)	16 (24.24%)	
T3	12 (44.4%)	11 (47.8%)	8 (50%)	31 (46.97%)	
T4	2 (7.4%)	1 (4.4%)	4 (25%)	7 (10.61%)	
Indeterminate	2 (7.4%)	1 (4.4%)	0	3 (4.55%)	

There was no difference between groups (P = 0.286), as well as renal function decrease regarding renal function during follow-up from pre- to post-surgery stages (P = 0.459)

(Table 6). All groups presented an increase of serum creatinine values after surgery (*P* = 0.001). It is worth highlighting that 98.5% of surgeries were radical nephrectomies.

The mean follow-up time was 97.6 months and the overall disease-free survival rate was 84.8%. There was no statistically significant difference of this variable among groups (Fig. 1). Recurrence-free survival was 89%, 91%, and 69% on groups (1), (2) and (3), respectively. Recurrence sites of disease are described in Table 7.

The analysis of the three combined groups revealed an overall survival of 79%, in a mean estimated follow-up period of 76 months (Fig. 2). Global survival was, respectively, 96%, 74%, and 56%, in groups (1), (2) and (3). The group of patients that were diagnosed with hematuria only, presented a statistically higher average survival than those in group (3) (*P* =0.005) and a higher tendency toward a longer survival period when compared to group (2) (*P* = 0.055). Cox regression analysis showed an increase in the death risk of 10.5 times when comparing group (3) to group (1).

Table 6. Creatinine and renal clearance

Features (SD)	Group 1	Group 2	Group 3	Total	*P*
Creatinine					
Preoperative	1.39 (±1.67)	1.12 (±0.35)	0.88 (±0.29)	1.17 (±1.0)	0.081
Postoperative	2.09 (±2.07)	1.43 (±0.54)	1.63 (±1)	1.73 (±1.43)	
Creatinine clearance					
Preoperative	66.9 (±23.3)	68.4 (±25)	85.4 (±22.4)	71.9 (±24.5)	0.001
Postoperative	47.7 (±21.1)	51.9 (±17.4)	64.7 (±64.4)	53.3 (±35.4)	

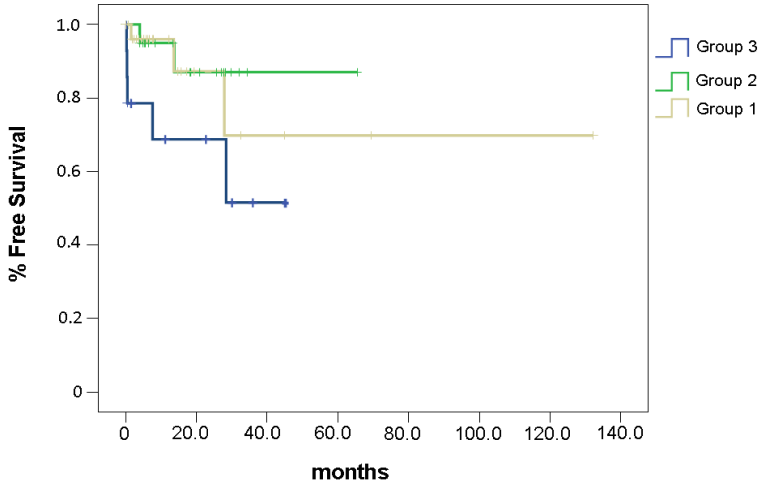

Fig. 1. Disease-free survival among groups

Table 7. Recurrence sites of the disease

Features	Group 1	Group 2	Group 3	Total
Recurrence				
Adrenal contralateral	1 (3.7%)	0	2 (12.5%)	3 (4.6%)
Lung	1 (3.7%)	0	3 (18.8%)	4 (6.1%)
Liver	1 (3.7%)	1 (4.3%)	0	2 (3%)
Brain	0	1 (4.3%)	0	1 (1.5%)
Peritoneum	0	0	1 (6.3%)	1 (1.5%)
Bladder	0	0	1 (6.3%)	1 (1.5%)
Bone	0	0	1 (6.3%)	1 (1.5%)
Indeterminate	0	0	1 (6.3%)	1 (1.5%)
N° of patients with recurrence	3 (11.1%)	2 (8.7%)	5 (31.3%)	10 (15.2%)

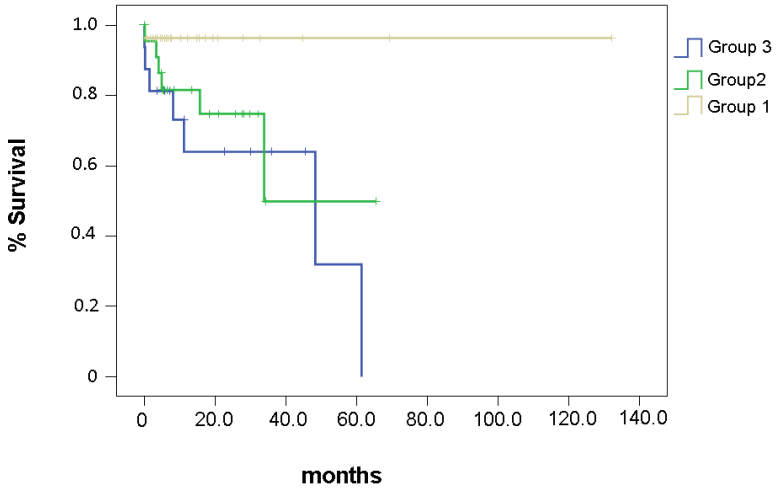

Fig. 2. Overall survival among groups

4. DISCUSSION

The incidental detection of kidney cancer has increased due to the dissemination of the use of abdominal imaging methods [12-15]; such tumors tend to be smaller when compared to symptomatic lesions, according to the observations of Siow et al. [16]. Our study indicated that lesions with isolated hematuria tend to present minor diameters than its counterparts presenting additional symptoms. Such finding may have implications in patients' prognosis, since other studies still point to the fact that lesion size is one of the most important prognostic factors for RCC [17].

Our patients had an average overall survival period of 79%, which are in accordance with results showed in previous studies [10-18]. Evaluating these groups separately, we observe that the association of two or more symptoms to hematuria has repercussions on the global mortality of patients, reducing the survival rate in 40%. Group (3) exhibits a risk 10.5 times greater of death than a patient in group (1).

The higher prevalence of kidney capsule and suprarenal invasion in group (3) correlates with the tendency that lesions presenting with more symptoms tend to be in a more advanced stage. Patard et al. [7] showed that this finding is more prevalent in a group of patients with systemic symptoms. Similarly, multivariate analysis showed that invasion of the perirenal fatty tissue is strongly associated with specific smaller cancer-specific survival in group (3).

Obviously, the higher prevalence of microvascular invasion and tumoral necrosis established in group (3) revealed to be a relevant finding in our study and it contributed for the worst survival rate in group (3), since microvascular invasion is an independent indicator of a worse prognosis, according to reports from different previous studies [10,11,19-21]. This also occurs in the presence of necrosis [22,23].

In our cohort we performed radical nephrectomy for T1 and T2 patients. Despite their smaller size, these tumors had unfavorable location to perform partial nephrectomy. This finding corroborates the fact that when hematuria is present a more aggressive tumor is usually found, even in smaller masses. In this study, the renal function deterioration shown within each group, both due to the increase of serum creatinine and the reduction of clearance only confirms an evolution already indicated in works that emphasize the impact of radical nephrectomy in urological and oncologic surgery on kidney function [24-26].

In a previous study, our group reported a recurrence-free survival rate of 82.9% for patients with incidental and 57.3% for symptomatic patients [11]. Schips et al. [9] showed that tendency when comparing asymptomatic patients with symptomatic patients upon the detection of RCC and proved that the presence of symptoms is a parameter of independent impact in the survival of these patients. Lee et al. [28] confirmed this finding in a retrospective analysis of 721 patients

submitted to nephrectomy for the treatment of RCC, reiterating that symptomatic presentation is a factor for independent worse prognosis. The main limitation of this study remains on its retrospective design, with its known disadvantages. Furthermore, patients without hematuria were not evaluated to make a comparative assessment. However, this work highlights the prognostic importance of symptoms in RCC patients.

5. CONCLUSION

In times of incidentally found kidney tumors, physicians should be alerted when caring for patients with hematuria, who may have worse outcomes. The association of two or more symptoms in patients with RCC has negative repercussions in the prognosis, with higher risk of death by the disease.

ETHICAL APPROVAL

As described in our methods section this study was approved by the Institutional Review Board of our institution under number 0178/10. The patients' informed consent was waived.

The last sentence in our methods section addresses ethical approval with similar message and is highlighted in yellow. If this section is required, you may delete the highlighted lines in our methods.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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