JBUON 2017; 22(6): 1434-1440
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Clinicopathological characteristics and survival in Serbian patients with renal cell carcinoma: a retrospective analysis

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Summary

Purpose: *Indications of kidney cancer outcome in lower-income countries are based on an incidence/mortality ratio due to lack of survival information. This study was conducted to provide outcome data in Serbian patients with renal cell carcinoma (RCC) and to identify prognostic factors that could affect their overall survival (OS).*

Methods: *This retrospective study included 185 patients who underwent nephrectomy. We assessed certain clinicopathological data including age, gender, tumor size, grade, stage and histological subtypes for their possible impact on OS.*

Results: *The 5-year OS was 63.2%. Significant association was found between OS and age (log-rank 12.455, p=0.006), tumor size (log-rank 26.425, p=0.000), grade (log-rank 13.249, p=0.000) and stage (log-rank 43.235, p=0.000). Univariate analysis indicated size (p=0.000), grade (p=0.001) and stage (p=0.000) as prognostic factors for OS. In multivariate analysis, grade (p=0.014) and stage (p=0.000) remained significant predictors of OS.*

Conclusion: *Tumor grade and stage were identified as independent prognostic factors of OS survival in Serbian patients with RCC.*

Key words: *kidney cancer, overall survival, prognostic factors, renal cell carcinoma, retrospective analysis*

Introduction

RCC is the most common malignancy among the different histological subtypes of kidney cancers. The incidence of RCC shows a spatial and temporal variation [1] and in the last two decades there was a constant annual increase incidence of 2% worldwide [2]. Several countries in Central and Eastern Europe show high rates of RCC incidence and mortality. According to currently available data in the period 1999-2014, Serbia is among European countries with relatively low rates for RCC with an average incidence of approximately 2% of all malignancies. However, in this 16-year period, the incidence was in constant increase accompanied by higher mortality rates [3]. RCC occurs slightly more often in men (1.5:1 ratio) with incidence peak between the 6th and the 7th decade of life [2]. In addition, it is characterized by lack of early warning symptoms (hematuria, flank pain and a palpable abdominal mass), which occur only in 10% of the patients and their presence is related to negative prognostic outcomes [4]. Widely accepted risk factors for RCC are cigarette smoking, male sex, hypertension and obesity [1]. Finally, between 2-4% of RCC cases are hereditary with the Cancer Genome Atlas Research Network reporting 19 mutated genes [5].

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Received: 14/04/2017; Accepted: 23/04/2017

RCC is comprised of a number of different histologically and genetically distinct types of cancer, classified into several subtypes. The most common subtypes include clear cell (ccRCC), papillary (pRCC) and chromophobe (chRCC), representing 70, 10-15 and 5% of all RCC cases, respectively [6]. These subtypes are associated with distinct clinical outcomes.

The 5-year relative OS for kidney cancer patients in Europe during 2000-2007 was 60.6%, in comparison to 72.4%, reported by Surveillance Epidemiology and End Results (SEER) data for 2004-2010 [1]. Prediction of GLOBOCAN 2012 till 2030 indicates an increase of kidney cancer incidence by 62% in low and medium income countries [7]. There is a lack of data regarding survival information for lower-income countries [1], including Serbia. Thus, we conducted this study to estimate the outcome data in Serbian RCC patients in relation to clinicopathological features and to identify prognostic factors that could affect their OS.

Methods

Patient information

Records were reviewed for 185 patients with RCC who underwent nephrectomy in several urology clinics in Belgrade, Serbia, between 2009 and 2013. We retrospectively analyzed the clinicopathological features of this cohort, including age, gender, size, grade, stage and histological classification. The 2004 WHO classification was used for tumor histology [6] and tumors were graded according to the Fuhrman grading system [8]. OS time was determined from the date of surgery until death or until the last follow-up appointment. Patients still alive or missed to follow-up were censored. The follow-up period was 5 years (range, 10-60 months). The average age of patients at diagnosis was 61 years (range 32-85).

Statistics

Statistical analyses were performed with SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Chi-square and ANOVA tests were used to compare qualitative and quantitative variables, respectively. The survival rate was calculated by Kaplan-Meier method and clinicopathological groups that included age, gender, tumor size, grade, stage and histological subtype were compared using log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to analyze the independent factors related to 5-year OS and p values <0.05 were considered significant.

Results

Clinicopathological findings

Clinicopathological characteristics of patients are displayed in Table 1. The majority of patients (66.5%) were between 50-70 years, and 57.8% of them were men. Tumor size ranged from 0.2-22.2 cm, with a median of 6.0 cm. The majority of tumors were up to 7 cm in diameter (67.6%). Low grade (I-II) RCC was diagnosed in 64.4% of the cases, while high grade (III-IV) tumors accounted for 35.6% of the patients. Stages 1 and 3 were most frequently recorded (42.2 and 38.4%, respectively) and ccRCC was the most common histological subtype at the time of diagnosis (73%).

Table 1. Clinicopathologicalcharacteristics of patients with renal cell carcinoma (n=185)

Characteristics	*n (%)*
Age (years)	
≤50	31 (16.8)
51-60	42 (22.7)
61-70	81 (43.8)
>70	31 (16.8)
Gender	
Male	107 (57.8)
Female	78 (42.2)
Size (cm)	
≤4	44 (23.8)
4.1-7	81 (43.8)
7.1-10	34 (18.4)
>10	26 (14.1)
Grade	
I	16 (8.7)
II	103 (55.7)
III	57 (30.8)
IV	9 (4.8)
Stage	
1	78 (42.2)
2	24 (13.0)
3	71 (38.4)
4	12 (6.5)
Histology	
Clear cell	135 (73.0)
Papillary	36 (19.5)
Chromophobe	14 (7.6)

The relationship between clinicopathological characteristics and histological subtype is depicted in Table 2. One hundred thirty-five (73%), 36 (19.5%) and 14 (7.6%) tumors were classified as ccRCC, pRCC (4 of type 1, and 32 of type 2), and chRCC, respectively. Significant association was found between histological subtype and gender (x^2=13.97, p=0.0009), and grade (x^2=12.61, p=0.0018). A male predominance was observed in ccRCC (58.5%) and pRCC (72.2%) tumors, whereas women had a higher frequency of chRCC subtype (85.7%). Grades 1 and 2 were found in 70.4, 38.9, and 71.4% of the three histological subtypes, respectively.

Table 2. Relationship between clinicopathological characteristics and histologic subtype in patients with renal cell carcinoma

Characteristics	*Clear cell n (%)*	*Papillary n (%)*	*Chromophobe n (%)*	*p*	x^2
Patients	135 (73.0)	36 (19.5)	14 (7.6)		
Age					
Mean (SD)	61.0 (9.9)	59.4 (11.9)	65.7 (5.3)	0.144#	
Gender				0.0009	13.97
Male	79 (58.5)	26 (72.2)	2 (14.3)		
Female	56 (41.5)	10 (27.8)	12 (85.7)		
Size (cm)				0.123	10.11
≤4	32 (23.7)	10 (27.8)	2 (14.3)		
4.1-7	65 (48.1)	8 (22.2)	8 (57.1)		
7.1-10	22 (16.3)	10 (27.8)	2 (14.3)		
>10	16 (11.9)	8 (22.2)	2 (14.3)		
Grade				0.0018	12.61
Low (I-II)	95 (70.4)	14 (38.9)	10 (71.4)		
High (III-IV)	40 (29.6)	22 (61.1)	4 (28.6)		
Stage				0.5799	4.722
1	56 (41.5)	16 (44.4)	6 (42.9)		
2	18 (13.3)	4 (11.1)	2 (14.3)		
3	51 (37.8)	16 (44.4)	4 (28.6)		
4	10 (7.4)	0 (0.0)	2 (14.3)		

One way-ANOVA

Survival analysis

Survival analysis revealed that 97.3, 78, and 63.2% of the patients were alive after 1, 3, and 5 years, respectively (Figure 1a). Statistically significant association was found between survival and age (log-rank 12.455, p=0.006), tumor size (log-rank, 26.425, p=0.000), grade (log-rank 13.249, p=0.000), and stage (log-rank 43.235, p=0.000) (Figure 1, b-e).

Regarding the association between age and OS, the highest 5-year OS rate was observed in the group of patients younger than 50 years (80.3%). Patients aged 51-60 had 1-, 2- and 5-year OS of 95.2, 85.4 and 77.5%, respectively; patients aged between 61-70 years had 1-, 2- and 5-year OS of 97.5, 69.2 and 56.3%, respectively; and those older than 70 years had 1-, 3- and 5-year OS of 96.8, 71 and 57.3%, respectively (Figure 1 b). The rates of OS after 1, 3 and 5 years for patients with RCC size ≤4 cm were 100, 85.4 and 82%, respectively; patients with tumor size 4.1-7 cm had survival rates of 98.8, 86.9 and 69.9% after 1, 3 and 5 years. After 5 years of follow-up, 56.6% and 22.6% of patients with RCC size 7.1-10 cm and >10 cm, respectively, were still alive (Figure 1c). Patients with low-grade tumors had longer OS than patients with high grade RCC. After 5 years, OS among patients with low-grade tumors was 70%. In the high-grade tumor group, the OS rate was 95.5, 64.6, and 51% after 1, 3 and 5 years, respectively (Figure 1d). Patients with low-stage tumors (stage 1 and 2) had OS rates of 79.1% and 80.9%, respectively, while 42.4% and 33.3% of patients with stage 3 and 4 were alive after a 5-year follow-up (Figure 1e). With regard to histological subtypes, the highest OS rate was observed in patients with chRCC (100% after 1 year and 76.2% after 3 and 5 years). Patients with the pRCC had the lowest OS rate, which was 53.5% by the end of the follow-up period, while the OS rates of ccRCC patients were 96.3, 78.1 and 66.3% after 1, 3, and 5 years, respectively (Figure 1f). In our group of patients, we found no significant association between histological subtype and OS rate (log-rank 2.088, p=0.352).

No statistically significant difference in OS was also noted with regard to gender (log-rank 0.855, p=0.355).

Univariate analysis (Table 3) showed that size (p=0.000), grade (p=0.001) and tumor stage (p=0.000) were significantly associated with OS. The grade (p=0.014) and stage (p=0.000) remained significant independent predictors of OS in multivariate analysis.

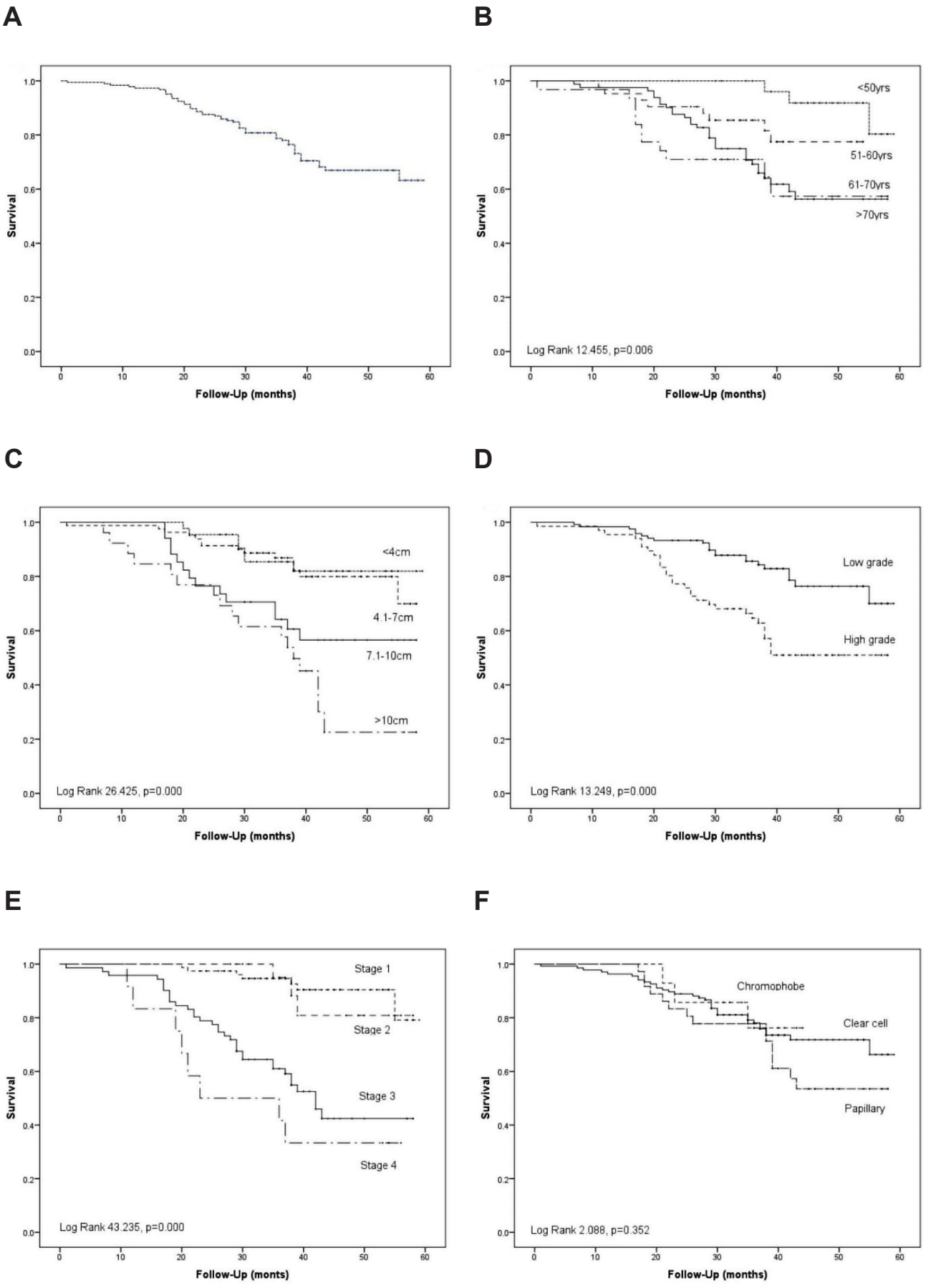

Figure 1. Kaplan-Meier curves for overall survival in 185 patients with renal cell carcinoma. **(A)** total survival; survival according to: **(B)** age, **(C)** tumor size, **(D)** Fuhrman grade, **(E)** stage, **(F)** histologic subtype.

Table 3. Univariate and multivariate analysis of factors affecting overall survival in patients with renal cell carcinoma

Variables	*Coefficient b*	*HR*	*95% CI*	*p value*
		Univariate analysis		
Age (years)				0.016
≤50		1.0	-	
51-60	1.0	2.7	0.7 - 10.3	0.142
61-70	1.7	5.2	1.6 - 17.3	0.006
>70	1.8	6.0	1.7 - 21.5	0.006
Gender				
Male		1.0	-	
Female	0.2	1.3	0.7 - 2.2	0.353
Size (cm)				0.000
≤4		1.0	-	
4.1-7	0.1	1.2	0.5 - 2.9	0.750
7.1-10	1.0	2.8	1.2 - 7.1	0.024
>10	1.6	5.0	2.1 - 12.1	0.000
Grade				
Low		1.0	-	
High	1.0	2.6	1.5 - 4.6	0.001
Stage				0.000
1		1.0	-	
2	0.3	1.3	0.3 - 5.1	0.682
3	1.9	6.9	3.1 - 15.6	0.000
4	2.4	10.7	3.9 - 29.6	0.000
Histology				0.362
Clear cell		1.0	-	
Papillary	0.4	1.5	0.8 - 2.8	0.170
Chromophobe	-0.1	0.9	0.3 - 2.9	0.861
		Multivariate analysis		
Grade				
Low		1.0	-	
High	0.7	2.1	1.2 - 3.7	0.014
Stage				0.000
1		1.0	-	
2	0.3	1.3	0.3 - 5.7	0.727
3	1.8	6.1	2.1 - 17.6	0.001
4	2.5	12.2	3.5 - 41.8	0.000

Discussion

The incidence of RCC has risen over the past decades, largely due to the utilization of ultrasonography, MRI, and CT scans. Prognostic factors for non-metastatic RCC include clinical, histological and molecular features, from which TNM stage and nuclear grade are among the most recognized ones [9]. Efforts are still carried out to find prognostic parameters for stratifying RCC patients into risk groups.

In this study it was not possible to retrospectively collect disease-specific deaths and, therefore, we used all-cause mortality as an endpoint. The 5-year OS in our study was ~63%, and it was within the range of current data [1]. In univariate analysis, tumor size, grade and pathological stage were independent predictors of OS. Notably, histological subtype of the primary tumor failed to be an independent predictor of OS. Age and gender were also not associated with OS in this cohort of patients. The tumor grade and stage remained

significantly associated with OS after multivariate analysis. These findings are in accordance with previous data since most authors agree that grade and tumor stage are the strongest independent prognostic factors for RCC [10]. Although there have been numerous grading systems for RCC, the Fuhrman system is most commonly applied. Furthermore, some studies indicated that the Fuhrman system has prognostic significance only when the data are grouped [11,12]. In our study, the RCC tumors were also grouped by low *versus* high grade. When we analyzed the data using grades separately (data not shown) we did not obtain statistical significance in survival prognosis. As indicated by Samaratunga et al. [12] these results are somewhat similar to Fuhrman's original report where grade 2 and 3 tumors were found to have similar survival with combined grades 2 and 3 tumors, differing significantly in outcome from grade 1 and grade 4 tumors.

Current literature shows that patients with stage 1 RCC have a 5-year disease-specific survival rate of 80-95%, and those with stage 2 of 75-95%. For patients with stage 3 RCC, a 5-year disease-specific survival is around 60% [13,14]. During the cytokine era, (1980s to 2006), patients with stage 4 RCC had a 5-year disease specific survival of less than 10%, with a median OS 16-20 months [14,15]. The development of targeted agents that largely replaced immunotherapy, has improved median OS of patients with stage 4 RCC in excess of two years [16]. Compared to those studies, our findings are similar for patients with stage 1and 2, as they had 79% and 81% 5-year OS, respectively. However, patients with stage 3 had an OS of 42% and those with stage 4 the disease had an OS rate of 33%.

Tumor size is an important determinant of the UICC/AJCC (International Union Against Cancer/American Joint Commission on Cancer) TNM pathologic stage that correlates with perinephric fat extension, renal sinus invasion, metastatic potential and RCC prognosis [12]. Concerning tumor size, in our analysis the tumors with worse prognosis were larger than 4 cm. The risk of death for patients with tumor size of 4.1-7 cm, 7.1-10 cm, and >10 cm was 1.2, 2.8, and 5.0-fold higher, respectively. Although tumor size was a prognostic marker affecting the survival, this parameter has not proved to be an independent parameter in multivariate analysis. It is likely that relatively small number of analyzed cases may have underestimated the prognostic effect of tumor size although other biological reasons cannot be excluded. Studies have shown that in patients with ccRCC, each 1 cm increase in tumor size enhanced the risk of high grade (3-4) tumors in comparison to low grade (1-2) tumors [17] by 25%.

In this study, the 5-year OS rates for patients with clear cell, papillary, and chromophobe RCC were 66.3, 53.5, and 76.2%, respectively. Nonetheless, histological subtype was not a significant predictor of survival, in both univariate and multivariate analysis. According to some authors pRCC is associated with significantly better outcome compared to ccRCC [18], but there are studies that have not determined the significant survival differences between pRCC and ccRCC [19]. The lower OS of pRCC than ccRCC in our study may partly be attributed to the fact that almost all patients were diagnosed with pRCC type 2. Compared with type 1, type 2 pRCC is considered more aggressive, and has a poor prognosis. In a study of Pignot et al. [20], the 5-year disease-specific survival rate was 92% for type 1 and 44% for type 2 pRCC. Regarding chRCC, most studies reported that patients with this subtype have a significantly increased 5-year disease-specific survival when compared to patients with ccRCC [21-23]. In other studies the disease-specific survival estimates varied and RCC histological subtype was not shown to be statistically significant in a multivariate analysis of risk [24, 25]. In a series of 4603 patients, Patard et al. [26] found that RCC subtypes had prognostic significance in a univariate setting; however, in multivariate analysis, the TNM stage and grade were independent prognostic factors.

In conclusion, the results of the current study identified grade and stage as independent predictors of OS in RCC patients. The prognostic significance of tumor size and tumor subtype were not confirmed in this cohort of patients. This report represents the original contribution to RCC research from Serbian Health Institutions related to clinicopathological parameters and their correlation with OS.

Acknowledgements

This work was financially supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant III 41027).

Conflict of interests

The authors declare no conflict of interests.

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