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Renal Cell Carcinoma: A 10-Year Retrospective Study

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BACKGROUND/AIMS
This study was conducted to investigate survival and its associated factors in patients with clear cell renal cell carcinoma (CCRCC).

MATERIAL and METHODS
This retrospective study recruited patients diagnosed with CCRCC in Shahid Rahnemoon Hospital, Yazd, Iran, followed them up from their presentation until their death or end of the study and examined their demographic information and clinical and tumor characteristics. Continuous variables were expressed as mean±SD, and univariate analyses of survival were conducted using the Kaplan–Meier method and log-rank test and multivariate analyses using the Cox regression model.

RESULTS
The study recruited 206 patients, including 132 males, with CCRCC and a mean age of 57.9 ± 13.6 years. During the follow up, 53.9% (n = 111) of the patients survived and data regarding the survival status of 24.3% (n = 50) patients were missing. The mean survival duration was obtained as 59.9 ± 2.7 months. The independent survival indicators were grade 4 (HR: 2.4, 95% CI: 0.4-5.7, $P = .02$), older age (HR: 4.14, 95% CI: 1.7-8.4, $P = .02$), and treatment method includes post-operative chemotherapy (HR: 4.9, 95% CI: 1.7-10.8, $P = .004$) and post-operative radiochemotherapy (HR: 8.4, 95% CI: 1.9-16.2, $P = .03$).

CONCLUSION
This study found survival to be negatively correlated with grade 4, older age, and treatment method, i.e. post-operative chemotherapy and post-operative radiochemotherapy.

Keywords: Renal cell carcinoma, clear cell renal cell carcinoma, prognostic factor, cancer, survival

INTRODUCTION

As the 13th most fatal cancer worldwide,[1] renal cell carcinoma (RCC) accounts for 90% of all kidney cancers.[2] In recent years, advanced abdominal imaging has shown increases in the incidence of RCC, especially in developed countries.[3]

The survival rate has been differently reported depending on the tumor characteristics. The prognosis of tumors that are limited to the renal parenchyma is excellent, resulting in a 5-year survival rate of up to 90%; nevertheless, the survival rate is below 10% in metastases despite using multimodal treatments.[4,5] The survival rate is affected by the histological subtypes of RCC, including clear cell renal cell carcinoma (CCRCC) as the most common with the lowest survival rate,[6] papillary RCC, and chromophobe RCC.[5]

Although the prognostic roles of demographic and tumor characteristics have been addressed in literature, effective factors in the survival of patients with CCRCC are to be determined.[7–14] Given the reported significantly-high mortality of this cancer,[1] the present research aimed at investigating the overall survival and its contributing factors in the patients.

MATERIAL and METHODS

Study Population

This observational retrospective study focused on RCC patients in Shahid Rahnemoon Hospital, Yazd, Iran. An experienced pathologist reexamined all the RCC samples referred to the pathology department from 2008 to 2018. This study

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included all the samples positive for CCRCC based on the 2016 WHO classification and diagnostic criteria.[15] Patients with metastatic CCRCC were excluded from the study. All the patients were followed up from the date of diagnosing their cancer until their death or the end of the study. This study was performed after receiving the approval of the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (SSU. 1398.3738).

Data Collection

The study variables included patient age, clinical presentation of cancer, tumor stage, tumor grade, tumor site (right or left kidney), tumor size (below 4 cm, and above 4 cm), perinephric fat invasion (PFI), treatment method, survival status, and time of death (if applicable). All of the data were collected from the hospital records. Tumor stage was evaluated based on American Joint Committee on cancer 8th edition,[16] and tumor grade was categorized according to Furman Grading System. Tumor size was evaluated based on pathologic findings.

Statistical Analysis

The continuous variables were expressed as their mean values. The Kaplan–Meier method was used to calculate the survival duration and the log-rank test to compare survival curves for the individual categorical variables. The significant variables determined using the log-rank test were inserted into the Cox proportional hazard model to determine their correlations with survival. The statistical analyses were performed in Statistical Package for the Social Sciences (SPSS) version 22 (IBM SPSS Corp.; Armonk, NY, USA), and $P < .05$ was set as the level of statistical significance.

RESULTS

General Characteristics

This study included 206 consecutive patients (64% male and 36% female) with CCRCC and a mean age of 57.9 ± 13.6 years. The most frequent symptoms included abdominal pain and hematuria. The tumor lay on the right side of the kidney in 49.55% of the patients, its size exceeded 4 cm in 68%, PFI was observed in 21.85% at the time of diagnosis, and grade I tumor and stage I cancer were, respectively, reported in 32% and 29%. Table I summarizes the clinical and tumor characteristics of the patients.

Survival

During the follow-up, 111 out of the 206 patients survived and the survival status of 50 was missed. The mean survival duration was obtained as 59.9 ± 2.7 months (95% CI, 51.5-62.2, Figure 1). According to the univariate analysis, the relationships of survival with the patients' age (95% CI, 52.6-63.2, $P = .02$, Figure 2), treatment method (95% CI, 52.4-63.1, $P < .001$, Figure 3), and cancer grade (95% CI, 53.5-64.7, $P < .001$, Figure 4) were statistically significant. The multivariate analysis showed the significant and negative correlations of survival with grade 4, age, and treatment method, i.e. post-operative chemotherapy and post-operative radiochemotherapy (Table 2).

In contrast to the multivariate analysis (Table 2), the univariate analysis showed statistically significant differences in the survival duration between genders (95% CI, 50.3-61.4, $P = .03$), tumor sizes (95% CI, 51.4-62.7, $P = .04$), cancer stages (95% CI, 51.0-62.1, $P < .001$), and PFI (95% CI, 53.4-64.2, $P = .01$).

Main Points

- The classical triad of presentation for Renal Cell Carcinoma includes gross hematuria, flank mass, and flank pain found in almost 20% of Iranian patients which is 2 times higher than developed countries.
- The mean survival of the patients with nonmetastatic Renal Cell Carcinoma in Iranian population is 59.9 months.
- Patents' age and tumor's grade are independent indicators for survival in patients with Renal Cell Carcinoma.
- Tumor's size and perinephric fat invasion may not independently affect survival of patients with Renal Cell Carcinoma.

TABLE I. Clinical Information and Tumor Characteristics

Factor	Number	Percent
Clinical manifestation		
Hematuria	53	26
Flank pain	46	22
Flank mass	18	9
Hematuria and flank pain and mass	46	22
Without symptom	43	21
Stage		
1	60	29
2	68	33
3	55	27
Missing	23	11
Grade		
1	66	32
2	60	29
3	23	11
4	16	8
Missing	41	20
Type of treatment		
Surgery	140	68
Surgery and chemotherapy	59	29
Surgery and chemotherapy and radiotherapy	7	3

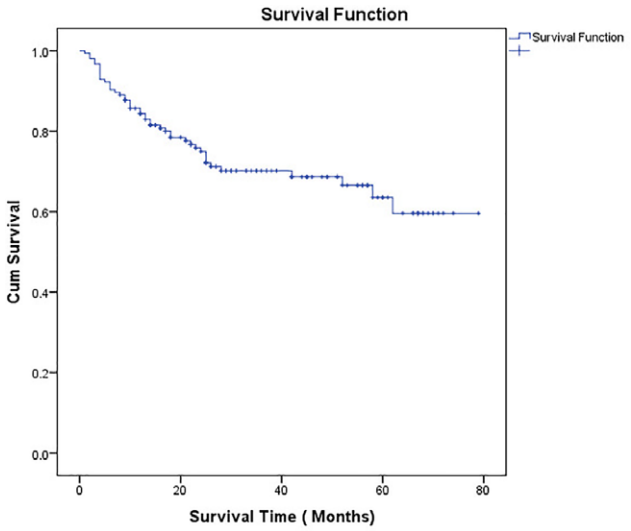

Figure 1. Curves of overall survival duration (month)

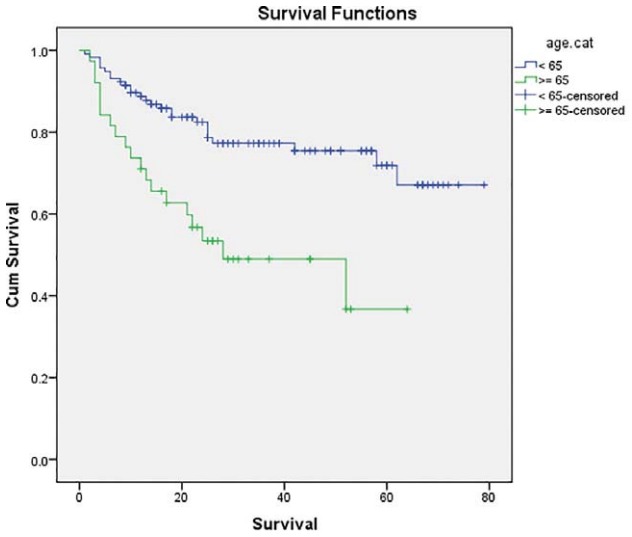

Figure 2. Survival duration (month) versus cancer grade

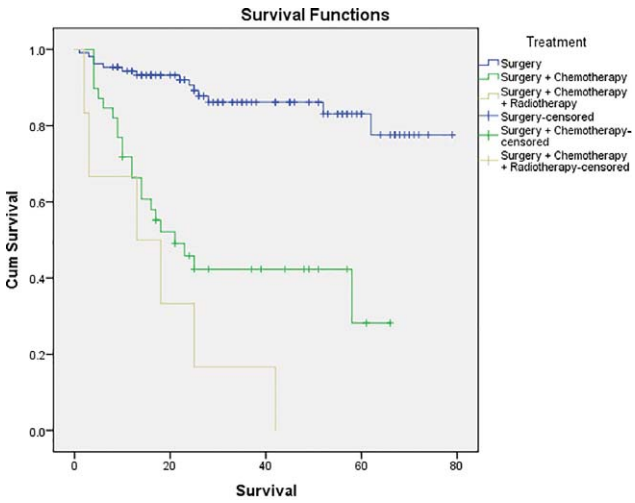

Figure 3. Survival duration (month) versus patient age

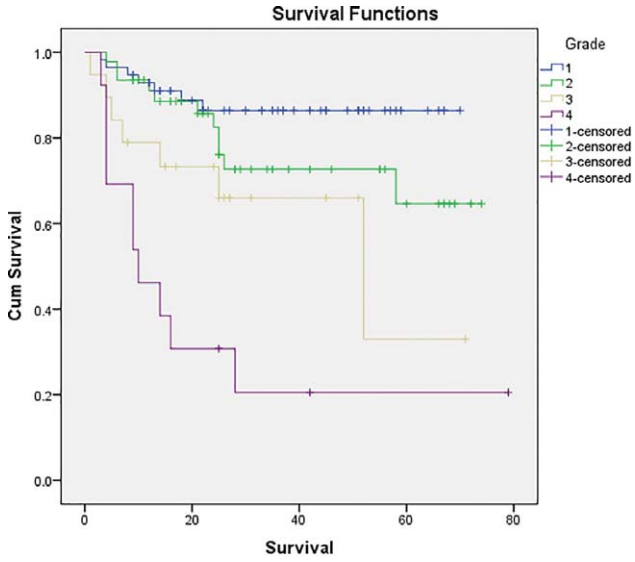

Figure 4. Survival duration (month) versus treatment method

TABLE 2. Survival Multivariate Analysis

Factors	HR (95% CI)	*P* value
Age cat		
<65	Reference	
>65	4.14 (1.7-8.3)	.02
Sex		
Male	Reference	
Female	0.6 (0.2-1.5)	.29
PFI		
No	Reference	
Yes	1.4 (0.5-3.6)	.47
Stage		
I	Reference	
2	1.1 (0.3-5.2)	.94
3	2.4 (0.4-6.8)	.68
Grade		
I	Reference	
2	1.5 (0.5-4.5)	.45
3	0.7 (0.1-3.6)	.12
4	2.4 (0.4-5.7)	.02
Tumor size		
≤4 cm	Reference	
>4 cm	1.7 (0.4-2.9)	.24
Treatment		
Surgery	Reference	
Surgery and chemotherapy	4.9 (1.7-10.8)	.004
Surgery and chemotherapy and radiotherapy	8.4 (1.9-16.2)	.03

DISCUSSION

RCC is the 6th and 10th most prevalent cancer in men and women, respectively.[2] Despite the improvements in screening methods and increased survival from localized cancers, a high mortality risk has been reported for this malignancy.[3,17] The histological subtypes and genetic characteristics of RCC are different. CCRCC is the most common subtype with the lowest survival rate compared to that of the other subtypes.[6,18] The present study was conducted to determine survival indicators in patients diagnosed with CCRCC.

The prognostic indicators of RCC were found to include the cancer stage, the tumor grade, and histological type of tumor.[19] The univariate model suggested the grade and stage significantly affect survival, and the multivariate model showed grade-4 tumors to constitute the determinant of survival. Investigating the TIN0M0 RCC prognostic factor in an Asian population, Zhang et al.[20] found the Fuhrman grade and tumor size to affect patient survival. Only nonmetastatic RCC included in this study, and this may be the probable cause for nonprognostic value of tumor stage in this study.

Research suggests significant correlations between tumor size and survival.[21–23] Cheville et al.[21] reported the mortality of tumors exceeding 5 cm in size to be 4.7 times higher. Bhindi et al.[23] reported positive correlations between tumor size and the risk of aggressive histology. The statistically significant correlations between tumor size and survival reported using the univariate model were also found to be insignificant based on

the multivariate model. Given the indirect effect of tumor size on survival through tumor grade, it was not an independent indicator of survival after adjusting tumor grade. Similarly, Thompson et al.[22] reported an increase of 25% in the risk of high-grade tumors with a 1-cm increase in tumor size.

The role of PFI in the survival of patients with RCC is still controversial. Despite the prognostic role of PFI reported in some studies,[24,25] its correlation with survival was found not to be independent after adjusting the tumor size.[26–28] Classical survival indicators do not include factors such as renal vein invasion and sinus fat invasion, which are often associated with PFI.[25] Kume et al.[25] found PFI to be correlated with aggressive tumor features and age. Cancer-induced mortality was higher in patients with PFI and even with small tumors. Hedgire et al.[4] found PFI to be an independent risk factor for cancer-specific survival even after tumor size adjustment. In contrast to the multivariate model, the univariate model of the present study showed PFI to constitute a risk factor for survival. Similarly, Ornellas et al.[29] found PFI to constitute a significant index for disease-free survival as per the univariate rather than multivariate model.

The potentially significant effect of age on survival has been addressed in literature in recent years.[30] The present study found age to constitute an independent indicator of survival in the patients. Scoll et al.[30] reported a negative relationship between the survival and tumor size (below 4 cm versus larger than 7 cm) in all age groups and found age to be a prognostic factor in medium-sized tumors (4-7 cm).

The classical triad of presentation for RCC includes gross hematuria, flank mass, and flank pain.[31] Advances in imaging and screening methods help with the earlier diagnosis of RCC even with asymptomatic tumors.[3,32] A 5-year survival was reported in 93% of patients with asymptomatic tumors and 59% with symptomatic tumors.[33] Research in western communities suggests the incidental diagnosis of almost 60% of patients with asymptomatic RCC, and that only 10% of the patients present with the classical triad.[5] Diagnosing the majority of the present study, patients with symptomatic tumors exceeding 4 cm in size can explain the lower mean survival of the patients with nonmetastatic RCC (59.9 months) compared to that in western populations (175.7 months).[34] It is therefore recommended that screening and clinical accuracy be improved in routine clinical practice to increase the survival rate in Iranian patients with RCC, and cancer studies be conducted at a national scale to acquire a broader perspective of RCC in Iran.

Treatment of patients is considered according to the stage of the disease and patients' age, so that patients in stages 1-3 are given priority with surgery. Surgery can be performed partially or radically so that patients in stage 1 and tumor size less than 7 cm are candidates for partial surgery. In tumors larger than 7 cm in size, radical nephrectomy is the treatment of choice.[35] In this study, our patients underwent partial and radical nephrectomy in stages 1-3. In patients with stage 3, based on patients' age and other factors influencing treatment choice, including cardiopulmonary status and comorbidities, radical nephrectomy with systemic therapy as well as radiation therapy was considered. Patients in advanced stage received radiation therapy, immunotherapy, and chemotherapy along with surgery if indicated. In this study, patients who received chemotherapy, radiotherapy, and surgery or patients received chemotherapy and surgery compare to patients who underwent surgery had a shorter lifespan. The probable explanation for this shorter lifespan could be other comorbidities rather than treatment itself. In the study of Goebell et al.,[36] they evaluate 1,085 patients with CCRCC. It is determined that high risk patients who usually excluded from clinical trials (ineligible-trial patients) because had significantly lower survival compare to trial-eligible patients and the type of treatment could not increase life expectancy.

The present study limitations included its unicenter and retrospective design, small sample and missing data, as well as failure to evaluate RCC subtypes other than CCRCC.

RCC was diagnosed mainly at its symptomatic stage, and its most prevalent clinical symptoms included abdominal pain and hematuria. The tumors identified mostly exceeded 4 cm in size. The present research found grade 4, age, and treatment method (post-operative chemotherapy and post-operative radiochemotherapy) to be independently and negatively correlated with survival.

Ethics Committee Approval: Ethical committee approval was received from the Shahid Sadoughi University of Medical Sciences, Yazd, Iran (SSU. 1398.3738).

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Conflict of Interest: The authors have no conflicts of interest to declare.

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