Oncological Outcomes of Chromophobe Versus Clear Cell Renal Cell Carcinoma: Results from A Contemporary Turkish Patient Cohort

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Purpose: To compare the oncological outcomes of clear cell RCC (ccRCC), which is common in renal cell carcinomas (RCC), and chromophobic RCC (chRCC), which is less common, and to define the factors affecting survival in the Turkish patient population for both RCC subclassifications.

Materials and Methods: Patients with a pathologically confirmed RCC diagnosis after radical or partial nephrectomy in the Turkish Urooncology Association (TUOA), Urological Cancers Database-Kidney (UroCaD-K), were retrospectively reviewed. Patients with ccRCC and chRCC were included in the study. The primary outcomes of this study are recurrence-free survival (RFS), overall survival (OS) and cancer-specific survival (CSS) for each histological subtype.

Results: Data from 5300 patients in the TUOA UroCaD-K are reviewed and a total of 2560 patients (2225 in the ccRCC group and 335 in the chRCC group) are included in the final analysis. In the comparison of the groups, tumor size was greater both radiologically and pathologically in chRCC (p = 0.019 vs 0.002 respectively). Recurrence-free survival (RFS), overall survival (OS) and cancer-specific survival (CSS) rates are worse in ccRCC subgroup. In the evaluation of risk factors; pathological stage, local invasion and Fuhrmann grade were found to be significant for recurrence in ccRCC. Age, body mass index and pathological stage were the risk factors affecting overall mortality (OM). Pathological tumor size was an independent risk factor for recurrence in chRCC, while age was analyzed as the only parameter affecting OM.

Conclusion: chRCC oncological data and OS, CSS and RFS rates were found to be better than ccRCC in the Turkish patient population.

Keywords: Kidney cancer; Chromophobe RCC; Clear cell RCC; Survival, Recurrence

INTRODUCTION

Kidney cancer is the second most common urinary tract cancer in the United States, resulting in approximately 73,750 new cases and 14,830 deaths in 2020[1]. In 2018, 403,262 new cases of kidney cancer were reported worldwide, two-thirds of which were predominantly male[2,3]. Clear cell renal cell carcinoma (ccRCC) is the most common histological subtype and occurs in 70% of cases. Chromophobe RCC (chRCC) is the third most common subgroup, constituting 5% of all RCCs[4].

The pathogenesis of chromophobe RCC develops from nephrons with distal convoluted tubules, unlike ccRCC that develops from proximal tubules[5]. Although chRCC is characterized by larger tumors, various surgical cohorts have been found to have a better-than-expected clinical course and metastasize less than other types of RCC[6-9]. We also looked at previous studies comparing cc-RCC with other RCC subtypes, papillary type2 RCC cohort demonstrated significantly lower CSS probability compared with selected cc-RCC cohort (2-yr CSS 72.8% vs 81.7%, 5-yr CSS 63% vs 72.4%, 10-yr CSS 31.5 vs 72.4%)[10], Radiological local invasion and age were found to be independent risk factors for recurrence and overall mortality, respectively for papillary type RCC and ccRCC groups. Likewise, pathological stage was also a risk factor for recurrence in ccRCC[11]. And the study that evaluated unclassified translocation RCC (tRCC) and cc-RCC patients, the authors reported the overall and cancer-specific mortalities were found to be higher in tRCC group[12].

The aim of this study was to compare recurrence-free

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Table 1. Clinical, pathological and oncological data of patients with clear cell RCC and chromophobe RCC.

		ccRCC (n=2225)	chRCC (n=335)	*p*
Age (year)		57.2 ± 11,8	54,8 ± 13,6	< 0.001
Sex, n (%)	Female	788 (35.6)	143 (42.9)	0,01
	Male	1425 (64.4)	190 (57.1)	
BMI (kg/m2)		28.1 ± 5	27.4 ± 4	0,428
Radyological tumor size mean(cm)		5.5 ± 3,3	6 ± 3.6	0,019
Tumor size, n (%)	<4cm	874 (39.4)	119 (35.5)	0,170
	4-7cm	795 (35.8)	117 (34.9)	
	7-10cm	378 (17)	63 (18.8)	
	>10cm	171 (7.7)	36 (10.7)	
Localised Disease, n (%)	Localised	1984 (89.2)	318 (94.9)	0.001
Locally advanced		241 (10.8)	17 (5.1)	
Patological tumor size (cm)		5.7 ± 3.3	6.4 ± 3.8	0.002
Patological T stage, n (%)	T1a	825 (37.1)	111 (33.1)	0.003
	T1b	632 (28.4)	106 (31.6)	
	T2a	242 (10.9)	47 (14)	
	T2b	91 (4.1)	26 (7.8)	
	T3a	290 (13)	28 (8.4)	
	T3b	19 (0.9)	1 (0.3)	
	T4	126 (5.7)	16 (4.8)	
Fuhrman Grade, n (%)	1-2	1118 (61.7)	- -	
	3-4	693 (38.3)	-	
T3-4 upstage, n (%)		314 (14.1)	40 (11,9)	0.282
Median follow-up time (months)		24.6 (1-165)	27.1(1-148)	0.546

survival (RFS), overall survival (OS) and cancer-specific survival (CSS) and define the risk factors for recurrence and OS for each group in patients diagnosed with chRCC and ccRCC in the Turkish Urooncology Association (TUOA), Urologic Cancer Database - Kidney (UroCaD-K).

MATERIAL AND METHODS

Patients with a pathologically confirmed RCC diagnosis after radical or partial nephrectomy in the Turkish Urooncology Association (TUOA), Urological Cancers Database-Kidney (UroCaD-K), were retrospectively reviewed. Patients with chRCC and ccRCC were included in the study. Recurrence and mortality status and survival (RFS, OS and CSS) data were analyzed. We have defined OS as patients who have died because of any reason during follow-up. CSS has been defined as patients who have died because of RCC or its treatment. And finally, RFS is defined as metastatic or local recurrence after initial treatment. Initially, clinical, pathological and oncological data were compared between the groups. Then, all data were evaluated to expose independent risk factors affecting recurrence and OM for each RCC group.

Histological subtypes were reported by expert genitourinary pathologists according to the guidelines of the International Union Against Cancer (UICC), the American Joint Committee on Cancer System 22 (AJCC), and the Heidelberg Classification[13]. The follow-up protocol of the patients was arranged according to the EAU-RCC guidelines.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical analysis

Study data were obtained from Research Electronic Data Capture (REDCap) electronic data tools hosted by TUOA. REDCap is a secure, web-based software platform designed to support data capture for research studies[14,15]. Analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22.0. Chi-square and Student *t*-tests were used to compare categorical and continuous data, respectively. The relationship between risk factors and histological subtypes was analyzed with logistic regression models. The Kaplan– Meier survival method was used to estimate tumor specific survival, and comparison was performed by the log-rank test. Multivariate Cox proportional hazard models were used to detect independent variables with a $p < 0.05$ considered to indicate statistical significance.

RESULTS

Data from 5300 patients in the TUOA UroCaD-K are reviewed and a total of 2560 patients (2225 in the ccRCC group and 335 in the chRCC group) with a mean age of 56.9 ± 12 years are included in the final analysis.

Clinical, pathological and oncological data of the patient groups and the comparison results are given in **Table 1**. Age and BMI were found to be higher in the ccRCC group from demographic data. Mean radiological and pathological tumor sizes were greater in chRCC than ccRCC. The rate of radiological local invasion was found to be higher in the ccRCC group (10.8% vs. 5.1%, $p = .001$). While the rate of pathological T3a-T4 patients was higher in the ccRCC group, the T2a-b ratio was higher in the chRCC group ($p = .003$). Median follow-up time and upstage rate were similar between the groups. Recurrence, overall mortality and cancer-specific mortality were found to be significantly higher in the ccRCC group. RFS, OS and CSS curves of the groups are given in **Figure 1**. OS and CSS were found to be better in chRCC than ccRCC. RFS was higher in chRCC patients, however, it was not reached statistically significance.

The factors affecting recurrence and overall mortality in the ccRCC and chRCC groups are given in **Table 2**. Accordingly, when we analyzed ccRCC patients for recurrence (n = 149), age (57.2 ± 11.8 vs 57. 5 ± 10.4, $p = .750$) and gender ($p = .588$) did not affect recurrence,

Table 2. Factors affecting recurrence and overall mortality in ccRCC and chRCC groups.

Histological Subtype	Recurrence Univariate P value	Multivariate OR (CI)	Overall Mortality Univariate P value	Multivariate
OR (CI)				
ccRCC				
• Age	0.750	-	< 0,001	1.067 (1.021-1.115)
• Sex	0.588	-	0.082	-
• BMI	0.006	-	0.013	0.830 (0.727-0.948)
• Patological tumor size	< 0.001	-	< 0,001	-
• Patologica stage	< 0.001	1,449 (1,155-1.817)	< 0.001	1.476 (1.096-1.986)
• Radyological invasion.	< 0.001	3.043 (1,267-7.307)	< 0.001	-
• Fuhrman 3-4	< 0.001	2.769 (1,187-6.458)	< 0.001	-
chRCC				
• Age	0.477	-	0.021	1.131 (1.007-1.269)
• Sex	0.203	-	0.184	-
• BMI	0.456	-	0.582	-
• Patological tumor size	0.013	1.195 (1.060-1.349)	0.744	-
• Patologica stage	0.095	-	0.107	-
• Radyological invasion	0.403	-	0.855	-

while low BMI (28.2 ± 4.9 vs 25.8 ± 4.8, p = .006), high pathological tumor size (5.5 ± 3.2 vs 8.6 ± 3.4, p < .001), radiological local invasion rate (9% vs 36.2%, p < .001), pathological stage (p < .001) and Fuhrman 3-4 rate (36.4% vs. 63%, p < .001) were found to be associated with recurrence. In logistic regression analysis, radiological local invasion (OR:3.043 (CI:1.267-7.307), p = .013), pathological stage (OR:1.449 (CI:1.155-1.817), p = .001) and Fuhrman grade (OR:2.769 (CI:1.187-6.458), p = .018) were determined as independent risk factors. When the overall mortality (n = 73) was evaluated, while gender (p = 0.082) was insignificant, advanced age (57 ± 11.8 vs 63±10.3, p < 0.001), low BMI (28.1 ± 4.9 vs 25.6 ± 4.7, p = .013), high pathological tumor size (5.5 ± 3.3 vs. 7.1 ± 3.3, p < .001), radiological evidence of local invasion (10.3% vs. 27,4%, p < .001), high pathological stage (p < .001) and Fuhrman 3-4 rate (37.3% vs 63.2%, p < .001) were among the factors affecting overall mortality. In logistic regression analysis, age (OR: 1.067 (CI: 1.021-1.115), P = .004), BMI (OR:0.830 (CI:0.727-0.948), P = .012), and pathological stage (OR:1.476 (CI: 1.096-1,986), P = .010) were found to be significant. While age (54.7 ± 13.7 vs 57 ± 9.2, P = .477), BMI (P = .456), gender (P = .203), radiological local invasion (4.9% vs 11.1%, p = .403) and pathological stage (p = 0.095) were similar for recurrence (n = 9) in chRCC, pathological tumor size (6.2 ± 3.7 vs 10.4 ± 5.4, P = .013) was found to be higher. In logistic regression analysis, only pathological tumor size (OR:1.195 (CI:1.060-1.349), P = .004) was found to be a significant risk factor. For overall mortality (n = 3), BMI (p = .582), gender (p = .184), pathological tumor size (6 ± 3.6 vs 5 ± 0.4, p = 0.744), radiological local invasion (p = .855) and pathological stage (p = .107) were similar, while advanced age (54.6 ± 13.5 vs 73 ± 6.6, p = .021) was significant. In the logistic regression analysis, only age (OR:1.131 (CI:1.007-1.269), P = 0.037) was found to be an independent risk factor.

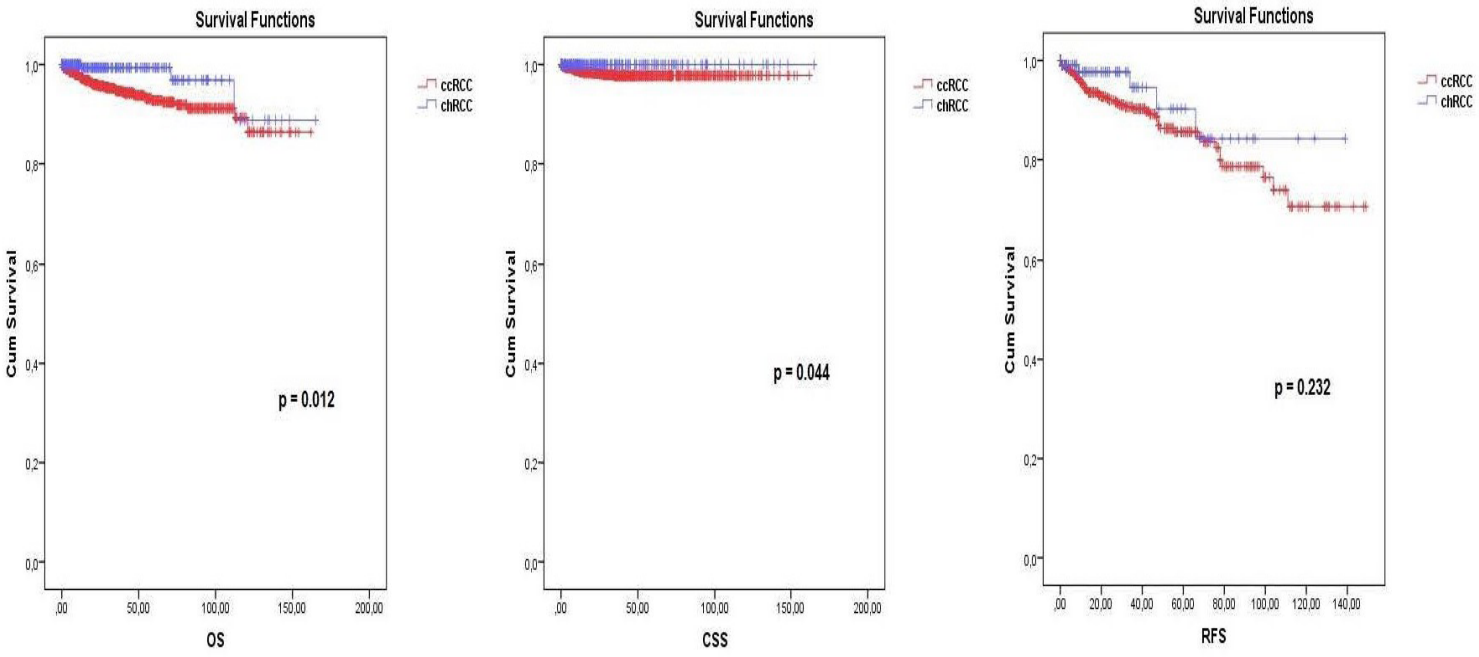

Figure 1. Curves of overall survival, cancer-specific survival, and recurrence-free survival for ccRCC and chRCC.

DISCUSSION

In this study, patients with ccRCC diagnosis showed more locally advanced disease, increased risk of recurrence and worse survival outcomes compared to chRCC. Considering the factors affecting recurrence and overall survival, pathological stage, local invasion and Fuhrmann grade were found to be independent risk factors for recurrence in ccRCC. Age, BMI and pathological stage were factors affecting overall mortality. Pathological tumor size was an independent risk factor for recurrence in chRCC, while age was analyzed as the only parameter affecting overall mortality.

For chRCC, 5-year recurrence-free survival and cancer-specific survival rates are 89.3% and 93%, respectively[7]. Taken as a localized disease, chRCC has a better prognosis than ccRCC[16-17]. Some studies suggest that chRCC is often curable with surgery alone, however, 5-10% of the patients with chRCC develop metastases during follow-up[7,18]. Patients with metastases from this rare variant are underrepresented in prospective phase III trials for standard and novel targeted drugs and the available data on medical treatment of chRCC patients is restricted[18-23].

Previous studies have tried to evaluate the oncological outcomes and predictive clinical parameters for survival in chRCC patients. The largest series of 291 cases were presented and reported gender, pathological tumor stage and sarcomatoid differentiation as predictors for reduced RFS and CSS[7]. Similar results concerning the relevance of pathological tumor stage and sarcomatoid differentiation were achieved by several study groups [24-27].

Recently, Frees et al. reported a direct comparison of OS and CSS results in chRCC and ccRCC cases, underscoring the favorable outcome of chRCC (28). An interesting characteristic of chRCC was also demonstrated in an analysis of the Surveillance Epidemiology and End Results (SEER) database: chRCC was most commonly seen in younger female patients within the non-clear cell RCC group[29].

Patard et al. reported that ccRCC 5-year survival rate was 73.2%, while this rate decreased to 10.5% in metastatic ccRCC patients. And the factors such as TNM stage, the tumor differentiation grade and the general clinical status were independent prognostic factors in multivariate analysis[30].

Casuscelli et al confirmed that chRCC is associated with a more favorable clinical outcome and a lower propensity for metastatic development than ccRCC. They also identified risk factors associated with metastatic development such as being large tumor and sarcomatoid differentiation[31]. But our results demonstrate the good prognosis of most chRCC with important exceptions metastatic disease and variant histology such as sarcomatoid differentiation.

Lack of standardization of surgeon/surgical technique and diversity of the pathological evaluation can be cited as the main limitations of the study. Failure to evaluate metastatic diseases and to evaluate survival outcomes with surgical treatment alone (not including systemic therapy) precluded assessment of true overall mortality and cancer-specific survival due to chRCC.

CONCLUSIONS

In the Turkish patient population; OS and CSS rates for chRCC were found to be better than ccRCC. In chRCC patients, high pathological tumor diameter and age were independent risk factors for RFS and OS, respectively. Radiological local invasion, advanced pathological stage and high Fuhrman grade were found to be associated with worse RFS. Also, age, BMI and pathological stage were related to OS for ccRCC patients.

CONFLICT OF INTEREST

None declared by the authors.

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