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ORIGINAL PAPER

Oncological outcomes of papillary versus clear cell renal cell carcinoma in pT1 and pT2 stage: Results from a contemporary Turkish patient cohort

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Summary *Objectives: To compare overall survival (OS), recurrence free survival (RFS), and cancer-specific survival (CSS) in the long-term follow-up of T1 and T2 clear-cell-Renal Cell Carcinoma (ccRCC) and papillary Renal Cell Carcinoma (pRCC) patients, as well as to determine the risk factors for recurrence and overall mortality.*
Material and method: Data of patients with kidney tumors obtained from the Urologic Cancer Database - Kidney (UroCaD-K) of Turkish Urooncology Association (TUOA) were evaluated retrospectively. Out of them, patients who had pathological T1-T2 ccRCC and pRCC were included in the study. According to the two histological subtype, recurrence and mortality status, RFS, OS and CSS data were analyzed.
Results: RFS, OS and CSS of pRCC and ccRCC were found to be similar. Radiological local invasion was shown to be a risk factor for recurrence in pRCC, and age was the only independent factor affecting overall mortality.
Conclusions: There were no differences in survivals (RFS, OS and CSS) of patients with localized papillary and clear cell RCC. While age was the only factor affecting overall mortality, radiological local invasion was a risk factor for recurrence in papillary RCC.

KEY WORDS: *Kidney cancer; Renal cell carcinoma; Clear cell RCC; Papillary type RCC; Recurrence, Survival.*

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INTRODUCTION

Almost twenty years ago the Heidelberg classification system recognized the histological subtypes of *Renal Cell Carcinoma* (RCC) as *clear cell* (cc)-RCC, with a frequency of 70-88% in most series, *papillary* (p)-RCC accounting for 10-15% and other RCC accounting for less than 10% (1, 2). Several studies have uniformly reported that a pRCC histology is associated with a favorable prognosis compared with *clear cell RCC* (ccRCC) (3-6). In other studies, pRCC was a significant risk factor (7, 8). However, the results of multivariable analyses assessing the prognostic significance of type2 pRCC histological subtype are incoherent (9, 10). In this context, outcomes may vary depending on the pRCC type and tumor stage.
The aim of this study was to compare OS, CSS and RFS of patients diagnosed with pRCC and ccRCC and define the factors affecting survival in the patient population with localized disease.

MATERIALS AND METHODS

Patients with *renal cell carcinoma* (RCC), who underwent radical or partial nephrectomy due to renal tumors, whose data were obtained from a series of 5300 patients with kidney tumors included in the *Urologic Cancer Database - Kidney* (UroCaD-K) of *Turkish Urooncology Association* (TUOA) were evaluated retrospectively. Pathological stage and grade were determined according to the *2002 Union Internationale Contre le Cancer TNM Classification*, and *Fuhrman classification* (G1-G4), respectively. Tumor size was measured using the *computed tomography* (CT) and taking the largest diameter.
Histological subtypes were classified according to the *Heidelberg* classification (1): ccRCC, pRCC, chromophobe, Bellini duct, and unclassified RCC. Patients from UroCaD-K database, who had pathological T1-T2 ccRCC and pRCC were evaluated in the study. According to the two histological subtype, recurrence and mortality status, *recurrence free survival* (RFS), *overall survival* (OS) and *cancer-specific survival* (CSS) data were analyzed. The follow-up protocol of the patients was arranged according to the EAU-RCC guideline.

Statistical analysis

Analyses were performed by the using of *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 tumor size and histological subtype was analyzed with logistic regression models. The Kaplan-Meier 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.

Table 1.
Clinical, pathological and oncological data of the patients.

		ccRCC (n = 1700)	pRCC (n = 429)	P
Age (year)		56.7 ± 12	59.6 ± 11.8	**< 0.001**
Sex, n (%)				
	Female	**641 (37.9)**	72 (16.8)	**< 0.001**
	Male	1048 (62.1)	**356 (83.2)**	
BMI (kg/m^2)		**28.3 ± 5**	27 ± 4	**0.004**
Radiological tumor size (cm)		5 ± 3	4.7 ± 3	**0.001**
Tumor diameter, n (%)				
	< 4 cm	787 (46.4)	226 (52.6)	**0.034**
	4-7 cm	626 (36.8)	126 (29.4)	
	7-10 cm	209 (12.3)	55 (12.8)	
	> 10 cm	77 (4.5)	22 (5.2)	
Radiological Organ confined, n (%)				
	Localized	1609 (94.6)	414 (96.5)	0.114
	Locally invasive	91 (5.4)	15 (3.5)	
Pathological tumor size (cm)		5±2.8	5.2±3.2	0.155
Pathological T stage, n (%)				
	T1a	806 (37.1)	216 (43.4)	**0.05**
	T1b	606 (28.4)	129 (25.7)	
	T2a	214 (10.9)	55 (11.6)	
	T2b	74 (4.1)	29 (6.3)	
Fuhrman Grade, n (%)	1-2	986 (70.4)	177 (67.8)	0.385
	3-4	413 (29.6)	70 (32.2)	
Relapse, n (%)		33 (1.94)	10 (2.33)	0.608
Overall mortality, n (%)		37 (2.17)	11 (2.6)	0.629
Cancer specific mortality, n (%)	10 (0.6)	2 (0.5)	0.556	
Mean follow-up time (months)	25.2 ± 30.3	26.1 ± 30.7	0.613	

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

Histologic subtype	Recurrence		Overall mortality	
	Univariate P value	Multivariate OR (CI)	Univariate P value	Multivariate OR (CI)
ccRCC				
· Age	0.958	-	**0.002**	1.056 (1.023-1.090)
· Sex	0.370	-	0.084	-
· BMI	0.279	-	0.471	-
· Pathological tumor size	0.071	-	0.105	-
· Pathological stage	**0.044**	1.447 (1.006-2.081)	0.091	-
· Radiological local inv.	**0.007**	4.136 (1.663-10.287)	**0.044**	-
· Fuhrman 3-4	0.952	-	**0.033**	-
pRCC				
· Age	0.444	-	**0.026**	1.066 (1.009-1.127)
· Sex	0.069	-	0.128	-
· BMI	0.270	-	0.131	-
· Pathological tumor size	0.776	-	0.275	-
· Pathological stage	0.423	-	0.474	-
· Radiological local inv.	**0.044**	7.808(1.507-40.450)	0.673	-
· Fuhrman 3-4	0.406	-	0.681	-

Results

The clinical, pathological and oncological data of the patients are shown in Table 1. Among 5300 patients, 2129 patients who had pathological T1-T2 ccRCC and pRCC were included in the study. The mean age was 57.7 ± 11.8 years and two-thirds of the patients were male. There were 1700 patients with ccRCC, while the pRCC was observed in 429 patients.

Patients in the ccRCC group were younger and had a higher BMI. (p values were < 0.001 and 0.004, respectively).

Radiological tumor size was statistically found to be smaller in pRCC than ccRCC group (mean size were 4.7 cm *vs* 5cm, p = 0.001).

We detected that radiologically < 4 cm tumors were more frequent in the pRCC group that ccRCC (p = 0.034). The finding of radiological local invasion was also more common in ccRCC, but there was no statistically difference (5.4% *vs* 3.5%). There was no statistically difference between the groups when we evaluated them in terms of pathological tumor size and Fuhrman grade. Considering the postoperative follow-up periods, the mean follow-up time for ccRCC and pRCC were 25.2 months and 26.1 months, respectively (p = 0.613).

Pathological T stage and radiological local invasion were found to be risk factors for recurrence in ccRCC. Age, radiological local invasion and Fuhrman grade 3-4 were found to be independent risk factors affecting overall mortality in patients with ccRCC. In pRCC patients, radiological local invasion was found to be an independent risk factor for recurrence and age was a risk factor for overall mortality (Table 2).

In addition, RFS, OS and CSS were not statistically different between the groups (Figure 1).

Discussion

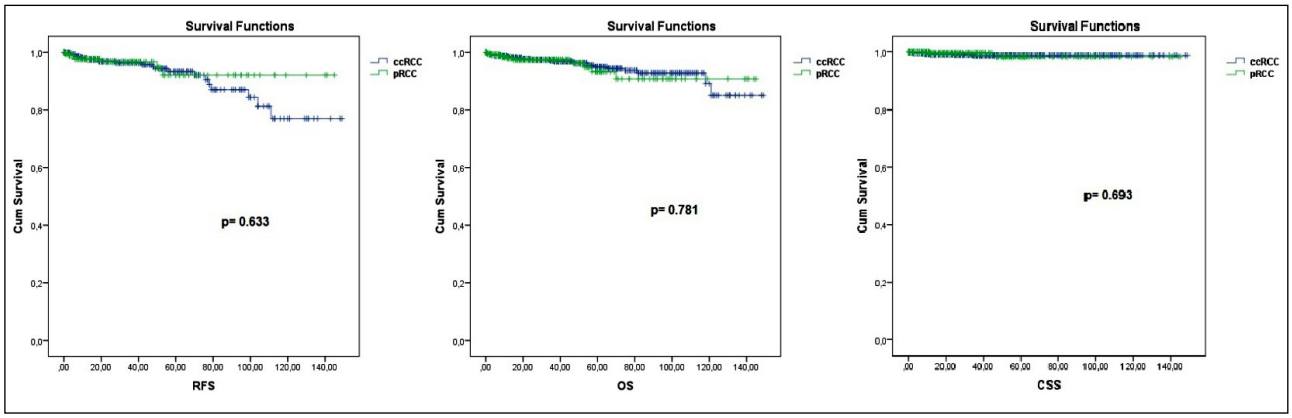
We aimed to discuss OS, CSS and RFS of patients diagnosed with pRCC and ccRCC and define the factors affecting survival in patient population with pT1 and pT2 disease. It was observed that ccRCC was seen in younger patients and in patients with higher BMI, and that pRCC was more common in males.

Papillary type pathology was radiologically smaller and was more frequently evaluated as pT1a than clear cell type. Radiological local invasion and age were found to be independent risk factors for recurrence and overall mortality, respectively for both groups. Pathological stage was also a risk factor for recurrence in ccRCC.

In addition, during the follow-up, OS, CSS and RFS were not statistically different for both groups in pT1 and pT2 disease.

The two most important factors determining the outcome of RCC are nuclear grade and tumor stage (11). According to some authors, apart from these two factors, histological subtype was also an independent prognostic factor (12).

Figure 1.
Kaplan-Meier Survival analysis of recurrence-free survival (RFS), Overall survival (OS), cancer specific survival (CSS) between pathological T1-T2 ccRCC and pRCC.



Type 1 pRCC is associated with MET alteration or trisomy of chromosome 7 where the MET gene is located, while Type2 pRCC shows allelic imbalance on chromosomes 1p, 3p, 5, 6, 8, 9p, 10, 11, 15, 18 and 22 (13, 14). According to the study shared by *Waldert et al.* 5-year CSS was 94% in type 1 pRCC and 74% in type 2 pRCC (p = 0.027). During the follow-up, the overall CSS for M0 patients with pRCC and ccRCC (90% *vs* 84% respectively) was not significantly different). *Steffens et al.* evaluated long-term survival of pRCC versus ccRCC. In this series, patients with pRCC had significantly higher 5-yr CSS rate (85.1% *vs* 76.3%; p = 0.001). Notably, at multivariable analysis, the papillary subtype was significantly associated with favorable oncologic outcome in localized RCC but was an independent negative prognostic factor in metastatic patients.
These results could be evaluated separately for papillary type 1 and type 2, but this was not evaluated in the study (14).
In addition, authors have shown that type 1 and type 2 RCC have similar clinical and histopathological features, but *lymphovascular invasion* (LVI) in type 2 pRCC worsened CSS rate, compared to type1 pRCC (5).
In a multicenter study involving more than four thousand patients from eight international centers, patients with pRCC had better 5-year CSS than patients with ccRCC in univariate analysis (73% *versus* 79% respectively). In multivariate analysis, the histological subtype was not an independent prognostic factor (15).
Five studies with 32.158 patients indicated that pRCC had a better prognosis than ccRCC (3, 6, 16-18), while other 5 studies including 3674 patients showed that pRCC was an independent predictor of poor outcomes (4, 7, 8, 19, 20). According to the results of the meta-analysis including these studies, pRCC was associated with better outcomes than ccRCC in patients with non-metastatic disease, but not in patients with metastatic disease. Type 2 pRCC had worse prognosis than ccRCC, but no significant difference was found with type 1 pRCC.
In this study, it was observed that the tumor size was smaller in pRCC. In the study of Waldert et al. tumor size was also smaller in pRCC (mean 4.5 cm) compared to ccRCC (mean 5.5 cm) (p = 0.013) (14).
Traditionally, p-RCC is divided into 2 types: type 1 is characterized by a basophilic cytoplasm and is classified as a low-grade tumor, while type 2 displays a bulky eosinophilic cytoplasm and pseudostratified tumor cell nuclei and is considered a high-grade tumor (3).
Compared to type 1 p-RCC, type 2 p-RCC presents more frequently as a locally advanced disease and is associated with more aggressive clinicopathologic features and significantly worse outcome (9, 10, 14, 21).
Our study had some limitations. Most important limitations are the retrospective analysis and the multi-centered design with pathological evaluation not performed in a single centre. Evaluation of the patients by experts in uro-oncology may reduce the disadvantage of multi-center data analysis. In addition, not taking into the account the pRCC subtypes can be considered among the limitations of the study.

Conclusions

In conclusion, RFS, OS and CSS were similar between pRCC and ccRCC patients with localized disease. Although it was not statistically significant, it is obvious that the histopathological and therefore cancer biology of the most common RCC subtypes are different. The management of patients should be planned according to the stage and subtype of the disease.

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