Oncological Outcomes of Patients with Non-Clear Cell Renal Cell Cancers: Subtypes of Unclassified and Translocation Renal Cell Cancers

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Purpose: We aimed to compare oncological outcomes in the two rare subtypes, unclassified renal cell cancer (unRCC) and translocation RCC (tRCC), vs clear cell RCC (ccRCC).

Materials and Methods: Between 2004 and 2019, from Turkish Urooncology Society Database, we identified 2324 patients for histological subtypes including 80 unRCC (3.4%), 19 tRCC (0.8%) and 2225 ccRCC (95.8%).

Results: The overall (15.8%) and cancer-specific mortalities (11.1%) were found to be higher in tRCC group and the recurrence free mortality (13.8%) was found to be higher in unRCC group. Larger pathological tumor size (p = 0.012) and advanced pathological T stage (p = 0.042) were independent predictive factors on overall mortality in patients with unRCC tumors.

Conclusion: The oncological outcomes of the unRCC and tRCC are worse than ccRCC and pathological tumor size and pathological stage are predictive factors for mortality in the unRCC.

Keywords: kidney; kidney cancer; oncology; pathology

INTRODUCTION

The majority of the kidney cancers are diagnosed histologically as renal cell carcinoma (RCC). The most common subtypes are clear cell RCC (ccRCC), chromophobe RCC (chRCC), and papillary RCC (pRCC). Other histopathological subtypes, including unclassified RCC (unRCC) and translocation RCC (tRCC), are rare and their frequencies are below 3% [1,2]. With increasing recognition of the morphological overlap between subtypes, the spectrum of morphological patterns in unclassified RCCs has widened and includes both low-grade and high-grade histological tumors[2]. Unclassified RCCs refers to a histologically heterogeneous tumor spectrum, many of which are high-grade, present with more frequent nodal involvement or distant metastasis, and are reported to have lower survival rates[1,3]. tRCC is a group of tumors characterized by recurrent rearrangements at the Xp11 locus or at the 6p21 locus[4]. Recently, the diagnosis of tRCC, which is frequently seen in childhood, increases in adults with a more aggressive behavior compared to children[5].

Treatment strategies for unRCC are depending on tumor stage, amenability to resection, and comorbidities, similar to ccRCC. The data of neoadjuvant treatments is still limited and adjuvant treatment for local advanced disease has not showed any benefit for overall survival in patients with unfovarable RCCs[6]. The optimal treatment of tRCC remains to be determined and recent data showed that tRCC commonly did not respond to immunotherapy and chemotherapy when compared to ccRCC[7]. In this study, we aimed to compare oncological outcomes in the two rare subtypes, unRCC and tRCC, vs ccRCC.

MATERIALS AND METHODS

Between 2007-2019, total of 2324 patients who had undergone radical or partial nephrectomy from 15 center due to renal cell carcinoma (RCC) were evaluated retrospectively. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at the Urologic Cancer Database - Testis,

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Table 1. Clinical, pathological and oncological data of patients with ccRCC, unRCC and tRCC.

		ccRCC (n=2225) (93%)	unRCC (n=80) (3.3%)	tRCC (n=19) (0.8%)	*p*
Age (years) [a]		57.2 ± 11.8	59.6 ± 10.8	34.5 ± 10*	< 0.001
Gender [b]	Female	788 (35.6)	28 (35.4)	12 (63.2)*	0.045
	Male	1425 (64.4)	51 (64.6)	7 (36.8)*	
BMI (kg/m^2) [a]		28.1 ± 5	29 ± 7.4	25.5 ± 2.6	0.231
Radiological tumor size (cm) [a]		5.5 ± 3.3	6.7 ± 4.5*	6.2 ± 2.3	0.003
Tumor diameter [b]	< 4cm	874 (39.4)	21 (26.3)	3 (15.8)	0.026
	4-7cm	795 (35.8)	31 (38.8)	12 (63.2)*	
	7-10cm	378 (17)	18 (22.5)*	2 (10.5)	
	>10cm	171 (7.7)	10 (12.5)*	2 (10.5)	
Tumor involvement b	Locally	1984 (89.2)	70 (87.5)	17 (89.5)	0.894
	Locally invasive	241 (10.8)	10 (12.5)	2 (10.5)	
Patological tumor size (cm) [a]		5.7 ± 3.3	7.6 ± 4.6*	6.5 ± 2.7	< 0.001
Pathological stage b	T1a	825 (37.1)	13 (16.3)	3 (15.8)	< 0.001
	T1b	632 (28.4)	16 (20)	10 (52.6)*	
	T2a	242 (10.9)	13 (16.3)	2 (10.5)	
	T2b	91 (4.1)	6 (7.5)	0 (0)	
	T3a	290 (13)	18 (22.5)*	0 (0)	
	T3b	19 (0.9)	2 (2.5)*	0 (0)	
	T4	126 (5.7)	12 (15)	4 (21.1)*	
Fuhrman grade [b]	1-2	1118 (61.7)	12 (20.3)	3 (42.9)	< 0.001
	3-4	693 (38.3)	47 (79.7)	4 (57.1)*	
Upstaging to T3-4 [b]		314 (14.1)	28 (35)*	2 (10.5)	< 0.001
Recurrence b		149 (6.7)	11 (13.8)*	0 (0)	0.025
Overall mortality b		73 (3.3)	8 (10)	3 (15.8)*	< 0.001
Cancer-specific mortality [b]		25 (1.1)	4 (5.3)	2 (11.1)*	< 0.001
Mean follow-up (month) [a]		24.6 ± 30.2	27.6 ± 31.6	16.1 ± 14	0.530

*The values showed statistically significance
[a] Data was expressed as mean and standard derivation
[b] Data was expressed as count and frequency

Turkish Urooncology Association (UroCaD-T). Patients with a solitary kidney, other urological diseases, and other malignancies were excluded from the study. Patients were divided into three groups as ccRCC, unRCC, and tRCC according to RCC histopathological classification. The pathological specimens were evaluated using the 2016 World Health Organization classification system. Demographic data including age, gender, BMI, tumor size, recurrence, and mortality status of the groups were collected from Redcap Database and compared. The recurrence-free survival (RFS), overall survival (OS) and cancer-specific survival (CSS) data were investigated. The Shapiro Wilk test was used for determining the normality. The continuous variables were shown as mean and standard derivation. The categoric variables were shown as count and frequency. The Chi-square test was used for comparison. The Kruskal-Wallis test was used for comparison and Mann Whitney U test was used for Post hoc test. Survival was analyzed using Kaplan-Meier estimate for histological subtypes between 2007-2019 and mean follow up for ccRCC is 24.6 ± 30.2 months. Uni- and multivariable Cox regression was used to analyze prognostic factors for overall survival (OS), recurrence-free survival (RFS) and cancer-specific survival (CSS). The variables entered the model as Age, Gender, BMI, Pathological tumor size, Pathological stage, Radiological T3-4 stage, Fuhrman 3-4. The p value of the model was meaningful for each group in first step.

RESULTS

We identified 2324 patients with RCC. The proportion of unRCC, tRCC and ccRCC in the 2324 patients were 80 (3.4%), 19 (0.8%) and 2225 (95.8%), respectively. Patient demographics are presented in Table 1. The mean age was lower, and the female ratio was higher in the tRCC group. Radiological local invasion rate, tumor diameter and pT3a/b ratio were higher in unRCC (12.5%, 6.7 ± 4.5 cm and 25% respectively). Fuhrman grade 3-4 ratio was also mostly observed in unRCC (79.7%). On the other hand, the pathological T4 stage rate was highest in the tRCC group (21.1%). Recurrences were found to be higher in unRCC group and no recurrence was observed in tRCC possibly due to relatively short follow-up periods in this group compared to the other groups (**Table 1**). The overall and cancer-specific mortalities were found to be higher in tRCC group (**Figure 1 and 2** and **Table 1**).

The predictive factors affecting recurrence and overall mortality in unRCC and tRCC groups are given in Table 2. The recurrence rate was 13.8% in unRCC group (**Table 1**) and none of the clinical and pathological factors were found to be statistically significant for recurrence in this group (**Table 2**). Overall mortality was 10% in unRCC group (**Table 1**) and larger pathological tumor size (HR:1.203. 95%CI:1.042-1.388. $p = 0.012$) and advanced pathological T stage (HR:1.517. 95% CI:1.015-2.268. $p = 0.042$) were found to be independent predictive factors for overall mortality in patients with unRCC tumors (**Table 2**).

Overall mortality was 15.8% in tRCC group (**Table 1**). Although, larger pathological tumor size was found to be a significant factor for overall mortality on univariate analysis (5.9 ± 2.4 vs 9.5 ± 3.1. $p = 0.035$), this factor was not found to be an independent factor for overall mortality after the multivariate analysis (HR:1.673 95%CI:0.958-2.920. $p = 0.070$).

DISCUSSION

The behavior and prognosis of non-clearcell RCC is varies. unRCC molecular characterization is particularly different from ccRCC, such as frequently seen mu-

Table 2. Predictive factors affecting recurrence and overall mortality in unRCC and tRCC groups.

Histological subtype	Recurrence		Overall Mortality	
	Univariate *p* value	Multivariate HR (CI)	Univariate *p* value	Multivariate
HR (CI)				
unRCC				
• Age (year)	0.548	-	0.304	-
• Gender	0.597	-	0.590	-
• BMI (kg/m^2)	0.338	-	0.841	-
• Pathological tumor size	0.070	-	0.043	1.203 (1.042-1.388)
• Pathological stage	0.216	-	0.031	1.517 (1.015-2.268)
• Radiological T3-4 stage	0.136	-	0.057	-
• Fuhrman 3-4	0.482	-	0.647	-
tRCC				
• Age (year)	-	-	0.177	-
• Gender	-	-	0.296	-
• BMI (kg/m^2)	-	-	0.460	-
• Pathological tumor size	-	-	0.035	1.673 (0.958-2.920)
• Pathological stage	-	-	0.419	-
• Radiological T3-4 stage	-	-	0.702	-
• Fuhrman 3-4	-	-	0.571	-

tations such as TP53, NF2, SETD2, and BAP1, while there are distinct differences such as lack of VHL alterations with unRCC[8,9].

But it is difficult to determine the histopathological type correctly and it can be determined by histomorphology, immunohistochemical and molecular genetic tests in selected cases. The literature makes comparisons of histopathological one subtype with ccRCC. Our study is an addition to literature because of compares subtypes within their self. In our study, the worst prognosis was seen in tRCC, when compared with unRCC and ccRCC.

Karakiewicz et al. reported that Fuhrman grade III-IV and metastatic disease were higher in unRCC compared to ccRCC (80% vs. 37.8% and 54.1% vs. 16.8%, respectively) and mortality rate was 1.6 times higher in patients with unRCC compared to ccRCC[2]. Additionally, a novel study which assessed 136 unRCC and divided four patterns included: predominantly oncocytoma/chromophobe RCC-like phenotype, predominantly papillary RCC-like phenotype, predominantly clear cell RCC- like phenotype, predominantly collecting duct-like phenotype, and pure sarcomatoid phenotype showed that he majority of the oncocytoma/chromo-

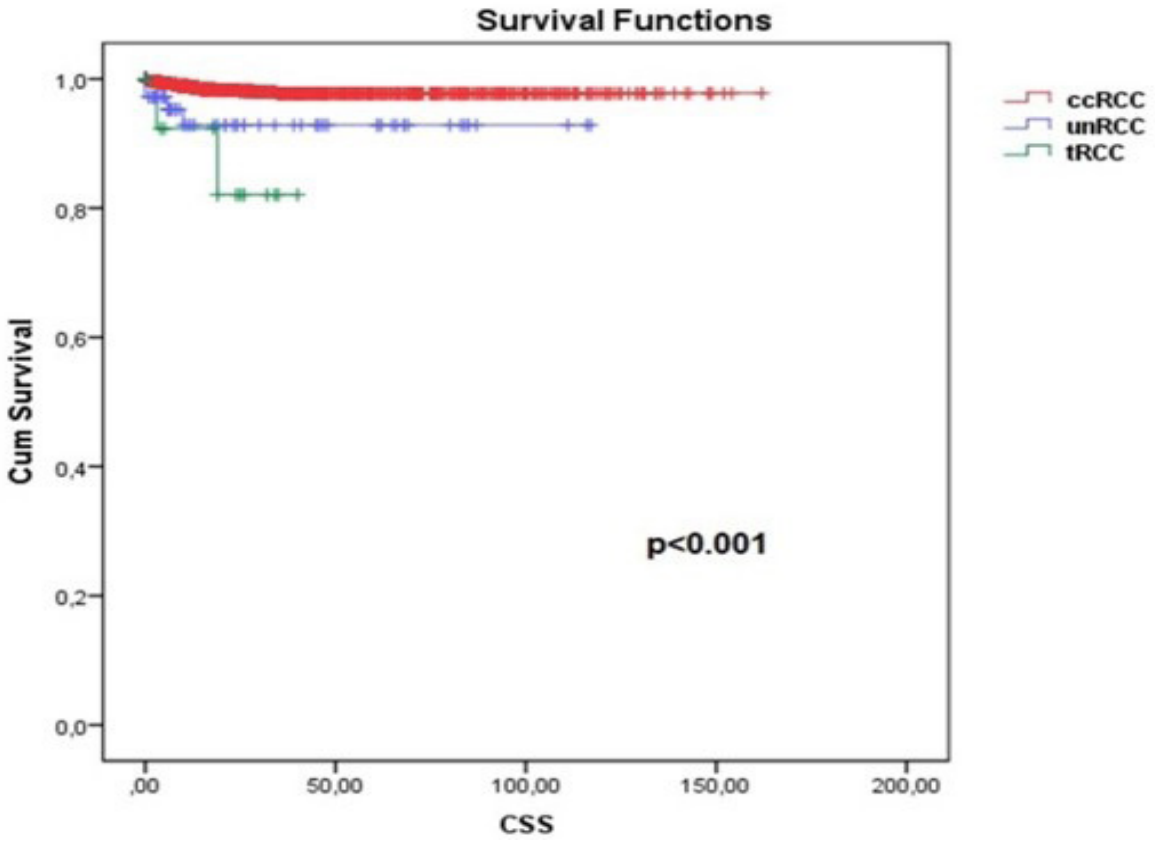

Figure 1. Cancer specific survival plots of ccRCC. unRCC and tRCC.

phobe and clear cell RCC-like phenotypes were low stage (pT1 or pT2). The papillary RCC-like, collecting duct-like, and pure sarcomatoid phenotypes were mostly high stage (pT3 or pT4)[10]. Controversially, Crispen et al. also reported that the Fuhrman grade III-IV was higher in unRCC group ($p < 0.001$) however, they found no difference in metastatic disease rate and overall survival rate between unRCC and ccRCC patients ($p = 0.239$, and $p = 0.345$, respectively)[11]. Additionally, a novel. study which assessed patients with unRCC showed that 58.8% of patients were in advanced stage and 76.5% had high Fuhrman grade[12]. In our study, like Karakiewicz et al, we found that unRCC had higher upstaging and local recurrence rates and worse cancer specific survival compared to ccRCC.

tRCC also had heterogeneity in oncological outcomes due to genetic heterogeneity. tRCC is a rare pathology and case series seen in childhood RCC and rarely adult age with an average age of onset of 50 years. The tRCC in childhood is generally considered mild prognosis[13]. The published studies pointed that the tRCC in adults had worse prognosis than papillary RCC and may be comparable or worse than clear cell RCC[14]. Campparo et al. reported that the rate of pT3-4 and metastatic disease were 30% and 42% in patients with tRCC. The recurrence rate was 32% and 16% of patients were died at a mean follow-up period of 29.5 months[15]. Similarly, our study showed that pT4 disease was higher in tRCC group and pathological tumor size was found to be a predictive factor for overall mortality both in tRCC and unRCC patients.

Limitations of the study: First, the lack of lymphadenectomy data and demographic data including comorbidities or smoking status is an important limitation. The literature demonstrated that the lymphnode dissection serves an important staging role by providing pathologic lymphnodestage, which has been independently associated with survival in nonmetastatic and metastatic renal cell carcinoma. However, literature also pointed that lymphnode dissection does not seem to provide a survival benefit for nonmetastatic or metastatic renal cell carcinoma, even in patients at increased risk for lymph node metastases. Second, our study is a multicenter study which represents the data of major urooncology institutions nationwide. Third, the absence of adjuvant treatment data is an important limitation regarding disease recurrence or progression, however due to the limited adjuvant treatment options in these rare histological subgroups, we believe this limitation should be accepted as a minor limitation.

CONCLUSIONS

Oncological outcomes of the tRCC and unRCC are worse than ccRCC. Pathological tumor size and pathological stage are predictive factors for mortality in the unRCC group. Pathological tumor size is also a predictive factor for overall mortality for tRCC.

SUMMARY

The rare histopathological subtypes, including unclassified RCC (unRCC) and translocation RCC (tRCC) have worse outcomes. Large pathological tumor size is found to be independent predictive factors for overall mortality in patients with unRCC tumors and tRCC. Addition-

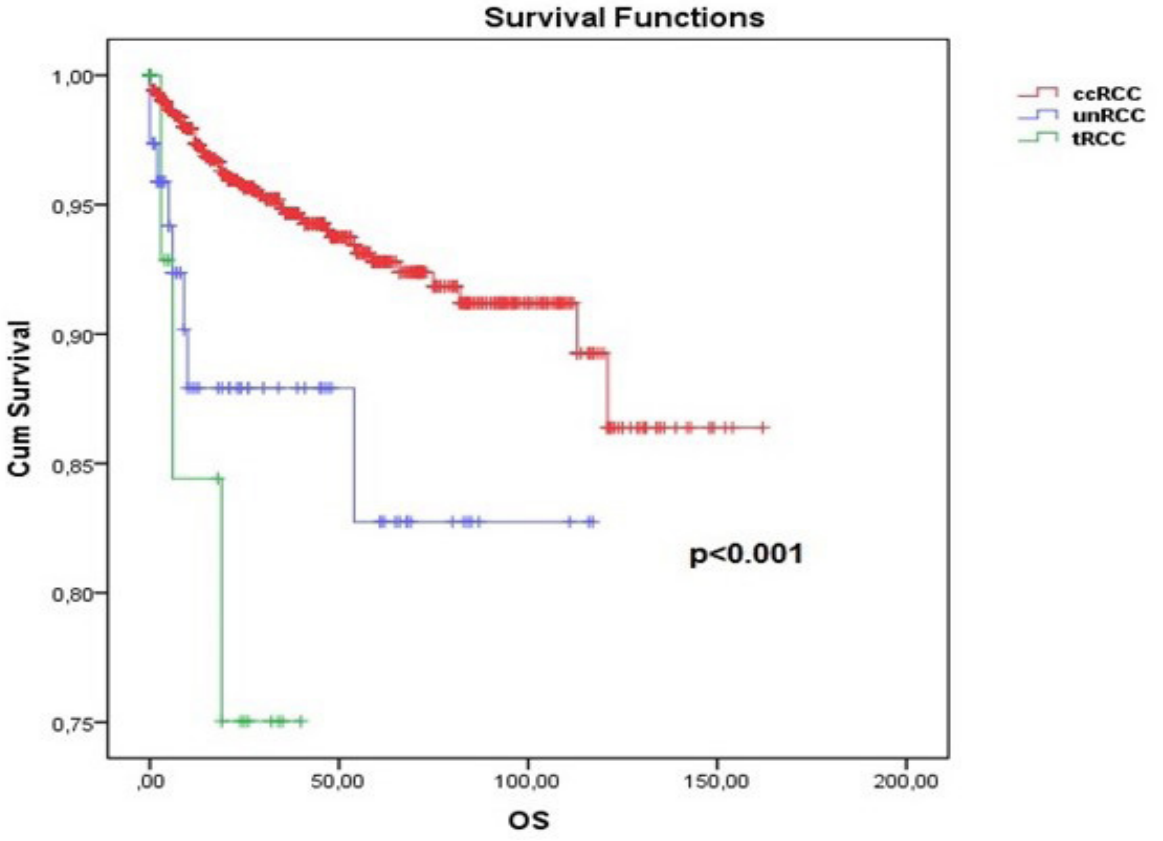

Figure 4. Overall survival plots of ccRCC, unRCC and tRCC

ally, advanced pathological tumor stage are found to be independent predictive factors for overall mortality in patients with unRCC tumors.

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CONFLICT OF INTEREST

The authors declared that there is no conflict of interest.

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