Characteristics and Prognostic Value of Papillary Histologic Subtype in Non-metastatic Renal Cell Carcinoma in Korea: A Multicenter Study

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Purpose: To analyze the characteristics of nonmetastatic papillary renal cell carcinomas (RCC) and the prognostic value of RCC histologic subtyping, based on a large multicenter experience in Korea.

Materials and Methods: A total of 2,905 patients with nonmetastatic RCC (TxN0M0) at the time of surgery were retrospectively enrolled from five institutions between 1999 and 2011 in Korea. Among these, patients with clear cell subtype (n = 2,488, 85.6%) and papillary subtype (n = 192, 6.6%) were included in our study.

Results: Patients with papillary subtype did not differ significantly from those with clear cell subtype on the following parameters: age (P = .694), gender (P = .511), body mass index (P = .136), patient performance status (P = .419), symptoms at presentation (P = .419), tumor size (P = .778) and pathologic stage (P = .367). However, high Fuhrman's grades were more common in papillary subtypes compared with clear cell subtypes (P = .001). The 5-year recurrence-free survival rates in patients with clear cell subtype and papillary subtype were 84.9% and 86.7%, respectively (P = .167). The 5-year cancer-specific survival rates in patients with clear cell subtype and papillary subtype were 92.0% and 93.1%, respectively (P = .931). Histologic subtype was not an independent prognostic factor of recurrence-free and cancer-specific survival (P = .107 and P = .998, respectively).

Conclusion: Our study suggests that the characteristics and prognosis of papillary subtype might be comparable to those of clear cell subtype in non-metastatic RCC, especially in Asia.

Keywords: kidney neoplasms; carcinoma; renal cell; papillary; pathology; follow-up studies; retrospective studies; prognosis.

INTRODUCTION

It is well known that renal cell carcinoma (RCC) is a heterogeneous and complex disease, and its natural history is greatly variable.[1] Prediction of disease progression is, therefore, critical in optimal clinical decision making with and counseling of patients. A variety of findings have been considered as prognostic factors for RCC. However, only a few prognostic factors including tumor-node-metastasis (TNM) stage, Fuhrman's grade and tumor size are almost undisputed prognostics factor for RCC, especially non-metastatic RCC.[2]

The histologic subtypes of RCCs, according to the 2004 World Health Organization (WHO) classification, include clear cell, papillary, chromophobe, collecting duct and unclassified.[3] Histologic subtype has been traditionally considered as a prognostic factor for RCC, based on molecular and genetic studies which have shown that RCCs have genetic and pathologic differences among the histologic subtypes.[4] However, the tumor characteristics and prognostic value of the histologic subtypes have not been verified, and remain debated.[2] It is also remarkable that almost all studies involving the prognostic value of histologic subtypes have focused on the Western population. Differences in characteristics of cancer among different races have well been established in other urologic cancers, such as prostate cancer.[5] Also, because many previous studies have reported the existence of racial/ethnic disparities in incidence and survival of RCC,[6-8] the prognostic value of histologic subtypes in Asians may differ from that in Westerners.

In the current study, we analyzed the characteristics and prognostic values of papillary RCC (pRCC) compared with clear cell RCC (cRCC) in nonmetastatic RCC, based on a large, multicenter experience in Korea.

MATERIALS AND METHODS

Study Subjects

Our study was a clinical case series with retrospective design based on a large, multicenter experience in Korea. A total of 2,905 patients with nonmetastatic RCC (TxN0M0), which was determined by imaging modalities at the time of surgery, were enrolled from five institutions

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Table 1. Association of different clinical and pathological variables with histologic subtype in non-metastatic renal cell carcinoma.

Variables	pRCC	cRCC	*P* Value
Number of subjects	192	2488	-----
Follow up duration, mean ± SD, months	38.0 ± 26.8	37.8 ± 29.7	.950
Age, mean ± SD, years	56.4 ± 13.5	56.1 ± 12.4	.694
Gender, no (%)			
Male	142 (74.0)	1785 (71.7)	
Female	50 (26.0)	703 (28.3)	.511
BMI, mean ± SD, kg/m^2	24.2 ± 3.4	24.5 ± 3.3	.136
ECOG PS ≥ 1, no (%)	114 (59.4)	1515 (60.9)	.678
Symptoms at presentation, no (%)			.419
No symptoms	156 (81.3)	2074 (83.4)	
Hematuria	16 (8.3)	235 (9.4)	
Flank pain	15 (7.8)	135 (5.4)	
Others	5 (2.6)	44 (1.8)	
Tumor size			
Continuous, mean ± SD, cm	4.3 ± 3.1	4.2 ± 2.9	.778
Category, no (%)			.225
< 4	112 (58.3)	1410 (56.7)	
4-7	43 (22.4)	682 (27.4)	
> 7	37 (19.3)	396 (15.9)	
Side, no (%)			
Left	105 (54.7)	1270 (51.0)	
Right	86 (44.8)	1207 (48.5)	
Bilateral	1 (0.5)	11 (0.4)	
Type of surgery, no (%)			.01
Radical nephrectomy	97 (50.5)	95 (49.5)	
Partial nephrectomy	1492 (60.0)	996 (40.0)	
Method of surgery, no (%)		0.067	
Laparoscopic	127 (66.1)	1799 (72.3)	
Open	65 (33.9)	689 (27.7)	
T stage (TNM 2002), no (%)			.367
pT1	151 (78.6)	1994 (80.1)	
pT2	20 (10.4)	203 (8.2)	
pT3	18 (9.4)	273 (11.0)	
pT43	(1.6)	18 (0.7)	
Fuhrman's grade, no (%)			.001
G1	7 (3.6)	166 (6.7)	
G2	86 (44.8)	1385 (55.7)	
G3	91 (47.4)	840 (33.8)	
G4	8 (4.2)	97 (3.9)	

Abbreviations: pRCC, papillary renal cell carcinoma; cRCC, clear cell renal cell carcinoma; SD, standard deviation; no, number of subjects; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status.

between 1999 and 2011. All patients had undergone surgery with curative intent. Patients with hereditary syndrome were excluded. Of the 2,905 patients identified, the 2,680 who were diagnosed with cRCC or pRCC, which are the 2 major histologic variants, were finally included in our study. One hundred thirteen patients underwent lymph node dissection, because of suspicious malignant lymph node lesions during the operation. However, all patients had pathologically N0. Thirty patients had positive surgical margins, and any of them did not receive any adjuvant treatments. After receiving approval from the relevant institutional review board (approval No. B-1202-145-102), patients' clinical and pathologic data were reviewed.

Variables

The following variables were noted in all patients: follow-up duration including recurrence-free survival (RFS) and cancer-specific survival (CSS), age, gender, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), symptoms at presentation, tumor size and laterality, type and method of surgery, pathologic stage, Fuhrman's grade and histologic subtype.

The follow-up consisted of a history, physical examination, comprehensive metabolic panel, abdominal computed tomography and chest radiography performed every 3 months for 6 months, every 6 months for 3 years and yearly after surgery for most of the patients. Bone or brain scan was performed only when clinically indicated. RFS and CSS were determined from the date of surgery to the date of recurrence and cancer-specific death, respectively, and identified using the imaging studies. Tumor size was determined from the pathologic specimen by recording the greatest diameter. Pathologic stage was determined according to the 2002 TNM classification system. Tumor grade was determined according to the Fuhrman's nuclear grade. Histologic subtyping was performed according to the 2004 WHO classification. To assess pathologic features, urological pathologists reviewed all specimens at

Table 2. Univariate and multivariate analyses predicting the probability of recurrence in non-metastatic renal cell carcinoma.

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.019	1.009-1.030	< .001	1.013	1.002-1.023	.020
Gender: Female vs. Male	0.935	0.715-1.222	. 621	0.976	0.742-1.282	. 859
BMI (kg/m^2)	0.932	0.896-0.969	< .001	0.941	0.903-0.980	.004
ECOG PS: ≥ 1 vs. 0	1.291	1.004-1.661	.047	0.816	0.624-1.067	.137
Symptoms at presentation	4.774	3.763-6.057	< .001	2.027	1.531-2.682	< .001
Tumor size	1.300	1.268-1.334	< .001	1.172	1.128-1.218	< .001
Side: Bilateral vs. Unilateral	1.584	0.394-6.369	.517	1.911	0.471-7.755	.365
T stage (2002 TNM)			< .001			< .001
T2 vs. T1	3.606	2.551-5.096	< .001	0.883	0.582-1.340	.558
T3 and 4 vs. T1	9.084	6.995-11.798	< .001	2.571	1.798-3.676	< .001
Fuhrman's grade			< .001			< .001
G2 vs. G1	1.948	0.788-4.813	.149	1.630	0.658-4.040	.291
G3 and 4 vs. G1	7.997	3.287-19.453	< .001	4.106	1.666-10.120	.002
Histology: pRCC vs. cRCC	0.686	0.401-1.175	.170	0.642	0.374-1.101	.107

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; pRCC, papillary renal cell carcinoma; cRCC, clear cell renal cell carcinoma.

each institution.

Statistical Analysis

To compare the relationship between clinical and pathologic characteristics of patients with cRCC and pRCC, independent *t*-test and Pearson's chi-square or Fisher's exact test were used in the comparison of continuous and categorical variables, respectively. The RFS and CSS rates were calculated using the Kaplan-Meier method, and the log-rank test was used to examine the difference in survival rate between two groups. The prognostic values of variables for survival were evaluated using Cox proportional hazards models. All tests were two-sided, and $P < .05$ was considered to be statistically significant. Statistical Package for the Social Sciences, version 17.0 (SPSS, Chicago, IL, USA) was used for all statistical assessments.

RESULTS

Histologic subtypes of all patients included the following; 2,488 (85.6%) with cRCC, 192 (6.6%) with pRCC, 158 (5.4%) with chromophobe RCC, 14 (0.5%) with collecting duct RCC and 53 (1.8%) with unclassified RCC. Mean age at surgery for all patients was 55.9 ± 12.6 years, and there were 2,040 males (70.2%) and 865 females (29.8%). Mean tumor size was 4.3 ± 3.0 cm, and the pathologic stage was T1a in 1,659 (57.1%), T1b in 628 (21.6%), T2 in 256 (8.8%), T3a in 306 (10.5%), T3b in 26 (0.9%), T3c in 5 (0.2%) and T4 in 25 patients (0.9%). Fuhrman's grade was grade 1 in 183 (6.3%), grade 2 in 1,548 (53.3%), grade 3 in 1.039 (35.8%) and grade 4 in 135 patients (4.6%).

Table 1 shows the association of different clinical and pathological variables between patients with cRCC and pRCC. Patients with pRCC did not differ significantly from those with cRCC for most variables. However, high Fuhrman's grades were more common in pRCCs than in cRCCs ($P = .001$). During the follow-up period, among 2,488 patients with cRCC, 258 (10.4%) had recurrence and among 192 patients with pRCC, 14 (7.3%) had recurrence. The 5-year RFS rates were 84.9 ± 1.0% in patients with cRCC and 86.7 ± 4.0% in patients with pRCC, and there was no significant difference between the two groups ($P = .167$, **Figure 1**). When patients were stratified according to pathologic stage, the 5-year RFS rates for cRCC and pRCC with T1 were 91.4 ± 0.9% and 94.1 ± 3.2% ($P = .095$), with T2 were 73.6 ± 4.1% and 87.7 ± 8.2% ($P = .321$), and with T3-4 were 47.5 ± 4.3% and 23.3 ± 19.3% ($P = .553$), respectively. When patients were stratified according to Fuhrman's grade, the 5-year RFS rates for cRCC and pRCC with grade 1 were 94.1 ± 2.8% and 100% ($P = .674$), with grade 2 were 92.9 ± 1.0% and 88.3 ± 6.3% ($P = .810$) and with grades 3-4 were 70.6 ± 2.2% and 84.6 ± 5.3% ($P = .020$), respectively. A significant RFS difference was only present among the two groups for Fuhrman's grade 3-4.

During the follow-up period, 129 patients (5.2%) with cRCCs and 10 patients (5.2%) with pRCC died of cancer-specific causes. The 5-year CSS rates were 92.0 ± 0.8% in patients with cRCC and 93.1 ± 2.6% in patients with pRCC, and there was no significant difference between two groups ($P = .931$, **Figure 2**). When patients were stratified according to pathologic stage, the 5-year CSS rates for cRCC and pRCC with T1 were 96.8 ± 0.6% and 97.8 ± 2.2% ($P = .209$), with T2 were 88.6 ± 2.9% and 84.6 ± 10.0% ($P = .764$) and with T3-4 were 62.5 ± 4.3% and 60.5 ± 16.0% ($P = .100$), respectively. When patients were stratified according to Fuhrman's grade, the 5-year CSS rates for cRCC and pRCC with grade 1 were 100% and 100% ($P = .850$), with grade 2 were 96.5 ± 0.7% and 100% ($P = .608$), and with grades 3-4 were 83.2 ± 1.9% and 87.5 ± 4.8% ($P = .357$), respectively. No significant CSS difference remained among the two groups stratified according to pathologic stage or Fuhrman's grade.

Independent prognostic factors of RFS in multivariate analysis were age, BMI, symptoms at presentation, tumor size, pathologic stage and Fuhrman's grade. However, the histologic subtype was not an independent prognostic factor of RFS in univariate and multivariate analysis ($P = .170$ and 0.107; hazard ratio (HR) = 0.686 and 0.642; 95% confidence interval (CI) = 0.401-1.175 and 0.374-

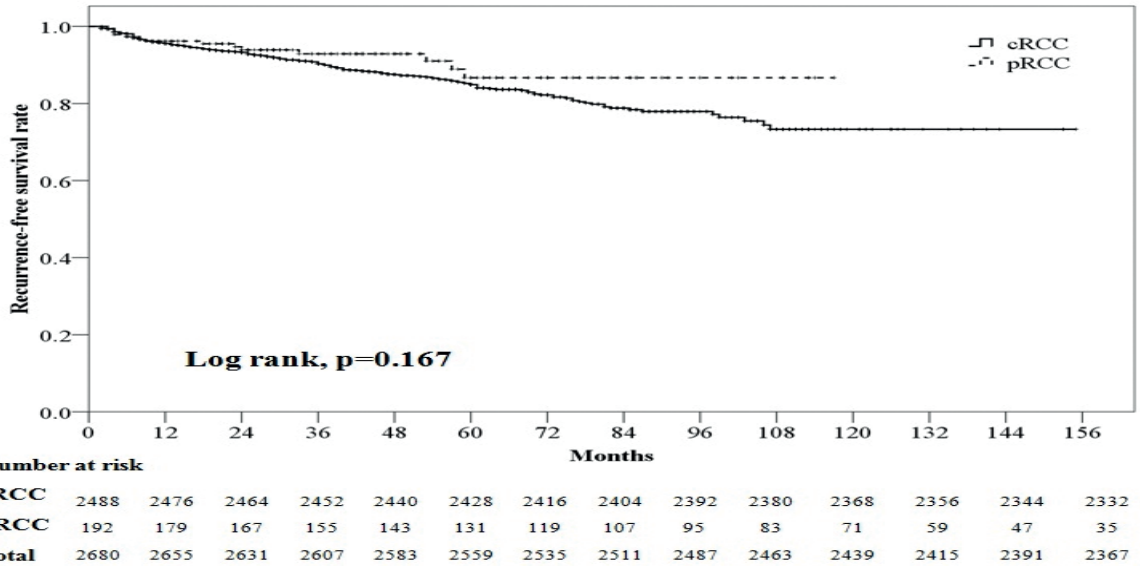

Figure 1. Kaplan-Meier curve for recurrence-free survival for patients with non-metastatic renal cell carcinoma according to histologic subtype.
Abbreviations: cRCC, clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma.

1.101, respectively (**Table 2**). Similar to those of RFS, independent prognostic factors of CSS in multivariate analysis were age, BMI, symptoms at presentation, tumor size, pathologic stage and Fuhrman's grade. The histologic subtype did not remain an independent prognostic factor of CSS in univariate or multivariate analysis *(P* = .931 and .998; HR = 1.029 and 1.001; 95% CI = 0.540-1.958 and 0.522-1.917, respectively (**Table 3**).

DISCUSSION

It is well known that histologic subtypes of RCC show differences in genetic and morphologic parameters.[4] Nevertheless, the characteristics and prognostic value of these histologic subtypes remain controversial.[2] Deng and colleagues[2] recently analyzed the data from large cohort studies including more than 20,000 patients. They

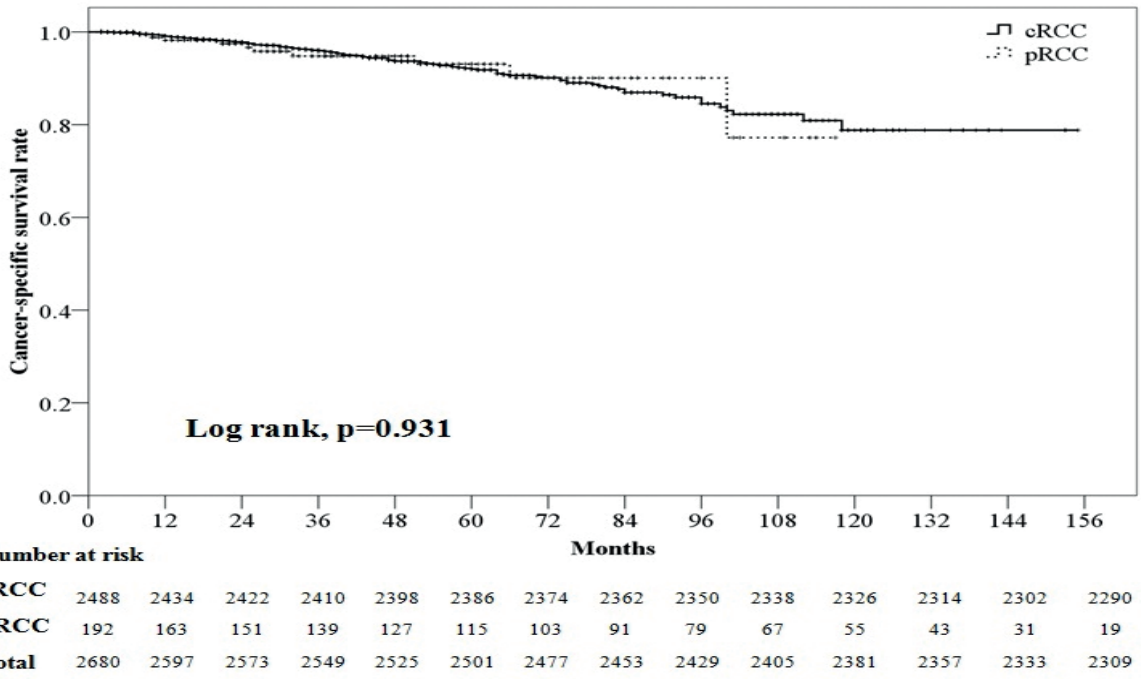

Figure 2. Kaplan-Meier curve for cancer-specific survival for patients with non-metastatic renal cell carcinoma according to histologic subtype.
Abbreviations: cRCC, clear cell renal cell carcinoma; pRCC, papillary renal cell carcinoma.

reported that the independent prognostic value of the histologic subtype is not yet widely accepted. Therefore, far more studies are needed to prove the prognostic value of histologic subtype.

Another important point is that almost all studies in this field have focused on Western populations. Differences in characteristics of cancer among different races have well been established in other urologic cancers, such as prostate cancer.[5] Racial disparities in RCC have also been reported in many studies. Using the national Surveillance, Epidemiology, and End Results (SEER) database, Vaishampayan and colleagues[6] reported that young blacks with localized renal cancer appeared to have had a greater rise in incidence and a poorer outcome than whites of the same age and pathologic stage. Tripathi and colleagues[9] also reported that race was a significant predictor of overall survival in metastatic RCC. Recently, Stafford and colleagues[7] published a large population-based study comparing racial/ethnic groups using 39,434 cases of RCC. They concluded that higher incidence rates and lower survival rates were identified among blacks when compared to their counterparts, whereas Asian/Pacific Islanders showed the opposite trend. RCC subtypes have also been reported to differ by race. Recently, Sankin and colleagues[8] reported that pRCC had a much higher occurrence among Blacks compared to non-Blacks. More recently, Purdue and colleagues[10] analyzed data from two large case-control studies of RCC, and observed a significant difference across RCC subtypes with respect to their distribution by race. Although the issue of race has not fully been established yet in RCC, the characteristics and prognostic value of histologic subtypes in Asians may differ from those in Westerners. Viewed in this light, our study is remarkable, because it is one of the largest population-based studies, especially in Asia.

pRCC generally accounts for approximately 10% of all RCCs, and is historically associated with smaller tumor size and presentation at an earlier stage and grade when compared with cRCC.[2,15,16] In our study, the distributions of cRCC and pRCC were 2,488 (85.6%) and 192 (6.6%) patients, respectively. The proportion of pRCC was slightly lower than that reported in previous studies performed on Western populations,[2] but it was similar to those performed on the Asian population.[11-14] In two studies of Japanese patients, the incidence of pRCC was 5.4 and 5.6%, respectively.[11,12] In a study of Chinese patients, the incidence of pRCC was 4.1%.[13] In a large multicenter study analyzing 2,981 Korean patients, the incidence of pRCC was also 5.6%.[14] Previous results including ours suggest that the proportion of pRCC in Asia might be lower than that in the West. From the viewpoint of tumor characteristics, opposite of our expectations, our results showed that there were no significant differences in the distribution of age, gender, tumor size, and stage between pRCC and cRCC. On the contrary, high Fuhrman's grades were even more common in pRCC. These trends are also similar to those in studies which were performed on the Asian population.[17-19] RCC is a heterogeneous and complex disease, and has genetic and molecular differences among the histologic subtypes.[1,4] Therefore, our results might reflect the characteristics of pRCC not in the West but in Asia.

Our results show that independent prognostic factors of RFS and CSS are age, BMI, symptoms at presentation, tumor size, stage and Fuhrman's grade. Of these factors, the most powerful predictors are stage and Fuhrman's grade. These results are similar to those reported in previous studies.[2,5] Stage represents the major prognostic factor used routinely in localized RCC.[2] The role of the Fuhrman's grade for pRCC is not widely accepted. However, recent studies have shown the prognostic value of Fuhrman's grade in pRCC. Klatte and colleagues[20] reported that Fuhrman's grade should be the standard grading system for pRCC. Zucchi and colleagues[21] also suggested that the use of Fuhrman's grade had prognostic relevance for pRCC. Our results also support the suggestion that Fuhrman's grade has the prognostic value for pRCC. The independent prognostic value of the histologic subtypes has not yet been verified. Although most previous studies have shown the prognostic value of histologic subtypes by univariate analysis, only a few studies have shown prognostic significance on multivariate analysis.[2] Teloken and colleagues[22] in a study of 1,863 patients with localized RCCs, showed that histologic subtype remained significantly associated with metastasis and CSS on multivariate analysis. However, the difference between pRCC and cRCC did not reach statistical significance. Recently, in a study of 3,062 patients, Leibovich and colleagues[23] reported that histologic subtype was an independent predictor of progression to distant metastasis and CSS. However, because these authors only analyzed the prognostic difference between cRCC and non-cRCC, the prognostic value of pRCC compared with cRCC is unclear. All of these large single center series have not proved that pRCC has a more favorable outcome than cRCC, when adjusted for covariates. Results from multicenter and international studies have also been similar to those from single center series. Patard and colleagues[15] analyzed 4,063 patients across the United States and Europe. They concluded that histologic subtype was not an independent prognostic factor of RCCs. In another multicenter study which included 2,530 patients in Europe, Karakiewicz and colleagues[24] reported that histologic subtype was not associated with outcome on multivariate analysis. Recently, Keegan and colleagues[25] published a very large multicenter study analyzing 17,605 patients using the SEER database. They reported that the effects of histologic subtype were decreased substantially after accounting for covariates. Particularly, the prognostic value of pRCC was not significantly different from that of cRCC. Similar to previous studies, our study has shown that the RFS and CSS of pRCC are not significantly different compared with those of cRCC. Both groups also have comparable RFS and CSS when stratified by pathologic stage and Fuhrman's grade except for grade 3-4. Based on univariate and multivariate analyses, histologic subtype is likewise not an independent prognostic factor. More recently, Steffens and colleagues[26] published a multicenter study in Germany. They reported that non-metastatic pRCC had a better prognosis compared with non-metastatic cRCC. However, it should be known that age, gender, stage and grade were only considered as a covariate.

Two distinct subtypes of pRCC were introduced in 1997, and are generally known to be associated with different clinical outcomes.[27] We could not assess the subtypes

of pRCC in our retrospective study. pRCC is heterogeneous,[28,29] and can show features characteristic of type 1 and 2.[30] Furthermore, many recent studies have not identified subtype as an independent prognostic factor.[30] Therefore, the prognostic value of subtype of pRCC is yet controversial. Nevertheless, it is a weak point that subtype of pRCC was not assessed in our study. Patients with lymph node and/or distant metastasis at the time of surgery were excluded, because natural history and treatments, such as targeted therapy of metastatic RCCs may be different from those of non-metastatic RCCs. Nevertheless, to our knowledge, our study is the largest Asian population-based study of the value of histologic subtype. Our results are noteworthy, because racial disparities in RCC have been reported in many studies,[6-10] and almost all previous studies have focused on the Western population.

There are a few limitations to our study. First, our data are retrospective in nature. Second, our study lacks a centralized pathologic review. Although most of the multicenter studies including ours have lacked centralized pathologic review, it is likely that this limitation has resulted in misclassifications or misdiagnoses. However, the proportion of pRCC in our study was similar to that reported previous studies performed on the Asian population, in which urological pathologists reviewed all specimens at each institution. Third, we could not assess potential prognostic factors, such as molecular markers, sarcomatoid features and tumor necrosis in all patients. These factors may better allow the identification of patients at high risk and affect the clinical outcomes. However, our study includes the most widely accepted independent prognostic factors of non-metastatic RCC, including stage, Fuhrman's grade, and tumor size,[2] and had one of the largest scale studies, especially in Asia.

CONCLUSION

Our results show that non-metastatic pRCC is not significantly different from non-metastatic cRCC in various clinical and pathologic parameters. RFS and CSS of non-metastatic pRCC are not significantly different compared with those of non-metastatic cRCCs, even when stratified by pathologic stage and Fuhrman's grade. In addition, histologic subtype is not an independent prognostic factor of non-metastatic RCC. Our study suggests that tumor characteristics and prognosis of pRCCs might be comparable to that of cRCCs, especially in Asia.

CONFLICT OF INTEREST

None declared.

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