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Morphologic subtyping as a prognostic predictor for survival in papillary renal cell carcinoma: Type 1 vs. type 2

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Abstract

Objective: To evaluate outcomes of surgically treated patients with clinically localized papillary renal cell carcinoma (RCC) and determine if papillary RCC subtype is associated with recurrence and survival.

Methods: This is a historical cohort study using the prospectively maintained Canadian Kidney Cancer Information System database between January 2011 and September 2018. All patients underwent partial or radical nephrectomy. Patient, tumor, treatment, and outcomes were compared between papillary RCC type 2 and type 1 cohorts.

Results: During the study period, 509 patients had clinically localized papillary RCC type 2 ($n = 172$) or type 1 ($n = 337$) histology. Sex, race, and comorbidities were similar between groups. Pathologic stage (pT3 or pT4), nuclear grade (3 or 4), and tumor diameter were higher in the type 2 papillary RCC cohort ($P < 0.0001$). A greater proportion of type 2 papillary RCC patients received radical nephrectomy (42.4% vs. 24.6%, $P< 0.0001$). More type 2 papillary RCC patients underwent lymph node dissection (19.6% vs. 5.5%, $P< 0.0001$) and had lymph node metastases removed during surgery (6.4% vs. 0.6%, $P= 0.103$). Overall, adjusting for age, grade, pathologic stage, positive nodes, and tumor size, type 2 papillary RCC had worse outcomes compared to type 1, as demonstrated by elevated all-cause mortality (hazard ratio = 7.7 [95% confidence interval: 2.0–28.9]), $P=0.0027$) and worse recurrence-free survival (hazard ratio = 8.2 [95% confidence interval: 3.6–19.0], $P< 0.0001$).

Conclusion: Patients with clinically localized type 2 papillary RCC present with higher risk disease and have worse prognosis compared to patients with clinically localized type 1 papillary RCC. To the best of our knowledge, this is the largest cohort study comparing papillary RCC subtypes.

Keywords: Carcinoma; Papillary renal cell; Subtyping; Survival; Prognostication

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Abbreviations: pRCC, papillary renal cell carcinoma; ccRCC, clear cell renal cell carcinoma; OS, overall survival; CKCis, Canadian Kidney Cancer Information System

1. Introduction

Papillary renal cell carcinoma (pRCC) is the second most common RCC subtype, accounting for 10% to 20% of all RCC cases [1]. pRCC is classified into 2 main subtypes: type 1 and 2 pRCC, based on histologic and cytogenetic features [1]. Type 1 tumors are typically multifocal with small cells containing basophilic cytoplasm while type 2 tumors have pseudostratified nuclei with large cells containing eosinophilic cytoplasm [2].

Despite its extensive molecular characterization, the prognostic implications of pRCC subtype on treatment and survival remains controversial. Several studies have reported significantly improved survival in patients with type 1 compared to type 2 pRCC, while other series have demonstrated that subtype does not independently predict prognosis [3–5]. Patients with type 2 pRCC are frequently diagnosed with larger tumors compared to type 1 pRCC, which may confound the association between subtype and prognosis [6–9]. However, differences in genetic alterations between pRCC subtypes may impact on the clinical phenotype of the tumors. Indeed, alterations of the CDKN2A, SETD2, TFE3, and FH genes are common in pRCC type 2 while mutations of the MET gene are common in pRCC type 1 [10].

To better understand the significance of pRCC subtype as a prognostic factor, we compared outcomes of patients with type 1 and type 2 pRCC using the prospective Canadian Kidney Cancer Information System (CKCis) cohort.

2. Methods

Data were retrieved from the prospectively maintained CKCis cohort which includes patients diagnosed with kidney cancer between January 1, 2011 and September 26, 2018 from 16 academic centers across Canada. This study was approved by the Hamilton Integrated Research Ethics Board. To be included in the study, all patients must have had nonmetastatic RCC at presentation which was subsequently confirmed as type 1 or 2 pRCC via tumor histology. While all centers had genitourinary pathologists, no central pathology review was performed.

In CKCis, demographic information such as age, sex, race, and comorbidities are captured at baseline. Disease characteristics are captured from imaging studies and pathology reports. Histologic subtype was determined from surgical pathology reports. Patients with mixed histology or unclassified papillary RCC were excluded. Treatment related information was obtained from the medical record. Outcomes, including postsurgical treatments, cancer recurrence, and death are updated at least every 12 months for nonmetastatic patients and every 3 months for metastatic patients. In this study, recurrence was considered any tumor recurrences outside of the kidneys.

Baseline information, including disease characteristics, was summarized and compared between type 1 and 2 pRCC using *t* tests or chi-squared test. The Kaplan-Meier method was used to estimate recurrence-free survival and overall survival (OS), which was defined as time of surgery to event. For recurrence, patients were censored at noncancer related death or last follow-up. For survival, patients were censored at last follow-up. The log-rank test was used for comparison between groups. Multivariate Cox proportional hazard models were used to adjust for potential confounders. A *P*value of 0.05 was considered statistically significant and no adjustment was made for multiple testing. Variables that were statistically significant in univariate analyses were subsequently used in multivariate analyses.

3. Results

3.1. Patient demographic

In total, 509 patients had clinically localized pRCC type 2 ($n = 172$) or type 1 ($n = 337$) histology. The mean age at surgery in the entire cohort was 61.9 (standard deviation 11.4) years. Patients in the type 2 pRCC cohort were older than the type 1 pRCC cohort at the time of nephrectomy (63.5 ± 10.8 years vs. 61.1 ± 11.6 years, $P = 0.027$). Sex, race, and medical comorbidities were similar between groups (see Table 1). Advanced pathologic stage (pT3 or pT4) (31.8% vs. 6.9%) and high nuclear grade (3 or 4) (75.5% vs. 17.6%) were significantly more common in type 2 compared to type 1 pRCC ($P < 0.0001$). The mean tumor size was larger in the type 2 pRCC cohort compared to type 1 [4.0 cm (interquartile range, IQR 2.7–6.5) vs. 3.5cm (2.3–5.3), $P = 0.007$].

3.2. Treatment characteristics

All patients included in the study received a partial or radical nephrectomy. A greater proportion of type 2 pRCC patients received radical nephrectomy as opposed to partial nephrectomy (42.4% vs. 24.6%, $P < 0.0001$). In total, 10% of all pRCC patients received some form of lymph node dissection. Lymph node dissection was more frequently performed in type 2 pRCC patients (19.2% vs. 5.3%, $P < 0.0001$). More type 2 pRCC patients had nodal metastases, although this was not statistically significant (6.4 % vs. 0.6%, $P = 0.103$).

3.3. Association between pRCC subtype and clinical outcomes

Among patients who were alive at the time of analysis, the median time of follow-up for type 2 pRCC and type 1

Table 1
Patient, tumor, and treatment characteristics

Characteristic	Type 1 pRCC ($N = 337$)	Type 2 pRCC ($N = 172$)	Total ($N = 509$)	P value
Mean age	61.1 ± 11.6	63.5 ± 10.8	61.9 ± 11.4	**0.027**
Gender, *n* (%)				0.082
Male	275 (81.6)	129 (75.0)	404 (79.4)	
Female	62 (18.4)	43 (25.0)	105 (20.6)	
Race, *n* (%)				0.151
Caucasian	219/246 (89.0)	103/123 (83.7)	322/369 (87.3)	
Non-Caucasian	27/246 (11.0)	20/123 (16.3)	47/369 (12.7)	
Median Charlson comorbidity index, score (IQR)	3 (1-4)	3 (2-4)	3 (2-4)	0.464
Nephrectomy, *n* (%)				
Partial	254 (75.4)	99 (57.6)	353 (69.4)	**<0.0001**
Radical	83 (24.6)	73 (42.4)	156 (30.6)	
Lymph node dissection, *n* (%)	18 (5.3)	33 (19.2)	51 (10.0)	**<0.0001**
pNX, *n* (%)	319 (94.7)	139 (80.8)	458 (89.9)	0.103
pN0, *n* (%)	16 (4.7)	22 (12.8)	38 (7.5)	
pN1, *n* (%)	2 (0.6)	11 (6.4)	13 (2.6)	
Median size of tumor, cm (IQR)	3.5 (2.3-5.3)	4.0 (2.7-6.5)	3.7 (2.5-5.5)	**0.007**
Tumor margin, *n* (%)				0.324
Positive	28/327 (8.6)	19/168 (11.3)	47/495 (9.5)	
Negative	299/327 (91.4)	149/168 (88.7)	448/495 (90.5)	
Nuclear grade 3 or 4, *n* (%)	54 (17.6)	120 (75.5)	174 (34.2)	**<0.0001**
Pathologic T3 or 4, *n* (%)	23 (6.9)	54 (31.8)	77 (15.1)	**<0.0001**

All p-values less than 0.05 were bold as they were considered statistically significant.

pRCC was 1.8 (IQR 0.7–3.4) years and 1.9 (IQR 0.6–3.9) years, respectively ($P = 0.941$). Significantly more type 2 pRCC patients developed metastatic disease (Fig. 1; hazard ratio [HR]: 8.03 [95%CI: 4.12–15.66], $P < 0.0001$). Subsequently, some metastatic type 2 and 1 pRCC patients received systemic therapy (60% vs. 42.9%, $P = 0.682$) or palliative radiation to metastases (34.3% vs. 0%, $P = 0.164$). Most metastatic RCC patients with type 2 or 1 pRCC received sunitinib as first-line systemic therapy (see Table 2). In the type 2 cohort, 8 patients with metastatic disease were enrolled in a clinical trial.

At the time of analysis, the median OS and recurrence-free survival were not reached for both groups. Compared to type 1 pRCC, patients with type 2 pRCC had increased risk of death (Fig. 2; HR: 5.5 [95%CI: 3.13–9.79], $P < 0.0001$) and recurrence (Fig. 1; HR: 8.03 [95%CI: 4.12–15.66], $P < 0.0001$). Adjusting for age, nuclear grade, pathological T stage, pathological N stage, and tumor size, pRCC subtype remained an independent predictor of OS (adjusted HR: 7.7, 95%CI: 2.0–28.9, $P = 0.0027$) and recurrence-free survival (adjusted HR: 8.2, 95%CI: 3.6–19.0, $P < 0.0001$).

4. Discussion

While there has been some disagreement in the literature, this cohort study supports the majority of evidence demonstrating that type 1 pRCC is a more indolent subtype compared to type 2 pRCC [10–23]. Clearly, knowledge of pRCC subtype is important for clinicians and patients, as this information is highly associated with prognosis.

While the differentiation in type 1 and 2 pRCC is clear on a pathological level, previous studies have not revealed whether this distinction is of clinical significance. Several contradictory studies have been published in the literature on the debate between the clinical significance of papillary subtyping. While multiple studies reported a significant difference in survival, showing less aggressive histopathological variables associated with type 1 pRCC, Yamanaka et al. [24] demonstrated no significant difference between type 1 and 2 pRCC across nearly all clinicopathological variables. Moreover, Mejean et al. and Pignot et al. showed no difference in aggressive features for type 2 pRCC compared to type 1 pRCC [21,25]. Concerning lesion size, Delahunt et al. [26] reported a significant difference between type 1 and 2 pRCC, but not in their study conducted in 2001 [27]. Our results are in accordance with the former as larger tumor size was observed in the type 2 cohort compared to type 1 (4.0 cm vs. 3.5 cm). The largest pRCC subtype series prior to the present study was by Bigot et al. (type 1 $n = 369$, type 2 $n = 117$), and included only patients treated with nephron-sparing surgery for T1-3 tumors. The results of this retrospective multi-institutional study reported patients with type 1 pRCC had an equal risk of RCC death compared to type 2 (HR: 0.9, $P = 0.89$) [28].

In this study of 509 cases of nonmetastatic pRCC with a considerably longer follow-up, pRCC type 1 was associated with better OS. In contrast to Bigot et al., our study demonstrated that pathological tumor stage and nuclear grade were the most important prognostic factors for RCC outcome. Pathologic stage (pT3 or 4) (31.8% vs. 6.9%, $P < 0.0001$) and nuclear grade (3 or 4) were significantly

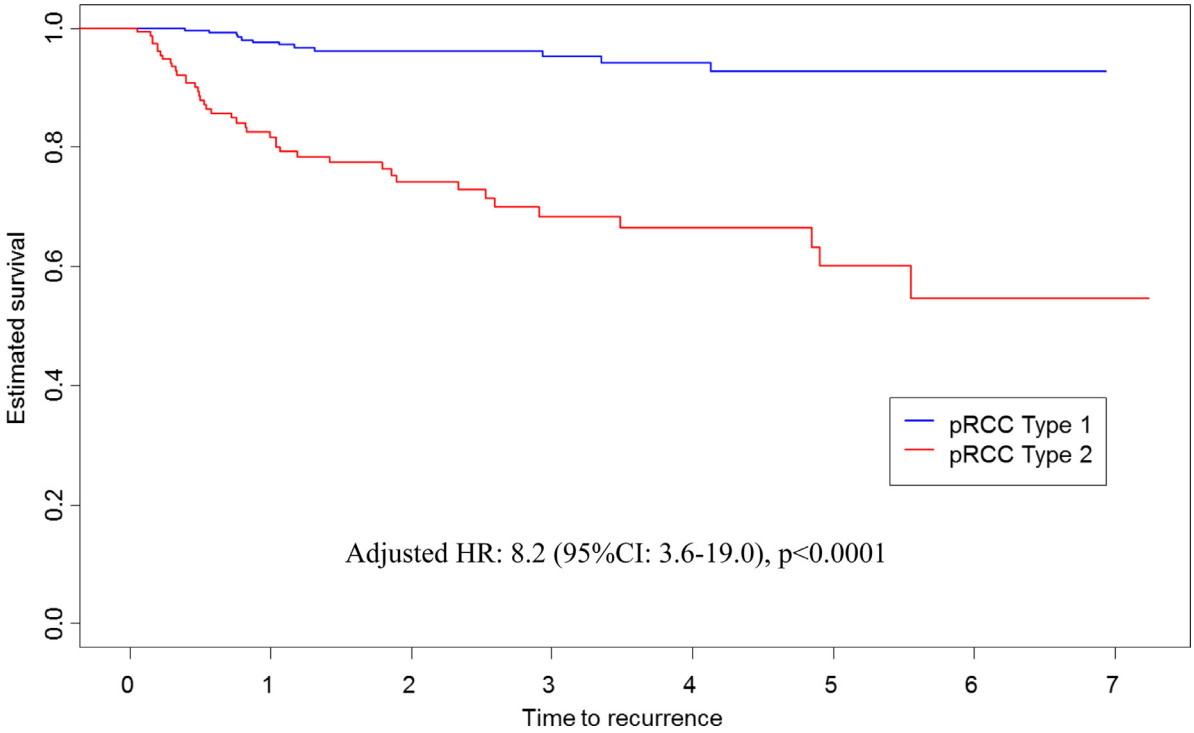

Fig. 1. Type 1 vs. type 2 pRCC in recurrence-free survival.

Table 2
Treatments used in the metastatic cohort

Characteristic	Type 1 pRCC (N = 7)	Type 2 pRCC (N = 35)	Total (N = 42)	*P* value
Systemic therapy, *n* (%)	3 (42.9)	21 (60.0)	24 (57.1)	0.682
Sunitinib	0 (0)	12 (34.3)	12 (28.6)	
Pazopanib	1 (14.3)	4 (19.1)	5 (11.9)	
Temsirolimus	2 (28.6)	2 (5.7)	4 (9.5)	
Crizotinib	0 (0)	1 (2.9)	1 (2.4)	
Pembrolizumab	0 (0)	2 (5.7)	2 (4.8)	
Clinical trial, *n* (%)	0 (0)	8 (22.9)	8 (19.0)	0.312
Radiation to metastases, *n* (%)	0 (0)	12 (34.3)	12 (28.6)	0.164
Bone-targeted therapy (Zometa), *n* (%)	0 (0)	1 (2.9)	1 (2.4)	1.0

higher in the type 2 pRCC cohort (75.5% vs. 17.6%, $P< 0.0001$). Again, similar to published literature, our results indicate that pRCC type 2 harbor more regional lymph node metastasis and distant metastasis at time of diagnosis, compared to patients with pRCC type 1. This may be owing to more clinically significant nodes in the type 2 cohort. Although median tumor size was small in the type 2 cohort, radical nephrectomy was more commonly performed due to nodal metastasis. In the present study, type 2 pRCC was associated with significantly poorer OS and recurrence-free survival compared to type 1 pRCC, in accordance with previous studies [11,12,18,21,29]. Consequently, our results support that not only should pRCC tumors be classified as type 1 and 2, but there remains significant clinical differences based on a patient's subtype.

Genomic alterations in pRCC subtypes, as demonstrated by The Cancer Genome Atlas Research Network, may account for differences in outcomes [10]. The group provided the molecular characterization of pRCC in a cohort of patients with predominately localized disease at diagnosis. In the study, the majority of type 1 tumors were characterized by alterations in the MET gene while type 2 tumors were characterized by alterations in several genes, including CDKN2A, SETD2, and TFE3 [30]. Findings from the study underscore the histological and morphological diversity of pRCC and demonstrate that several distinct subgroups exist within type 1 and 2 pRCC. Specific subgroups in type 2 pRCC have been associated with poor clinical outcomes. One such subgroup includes tumors exhibiting the CpG island methylator phenotype, which has been implicated in DNA hypermethylation. While CpG island methylator phenotype is not unique to pRCC, it may be a useful prognostic indicator [31]. More recently, Pal et al. analyzed a cohort of patients with pRCC. Further, 61% of these patients had metastatic disease at diagnosis. In the study, genomic

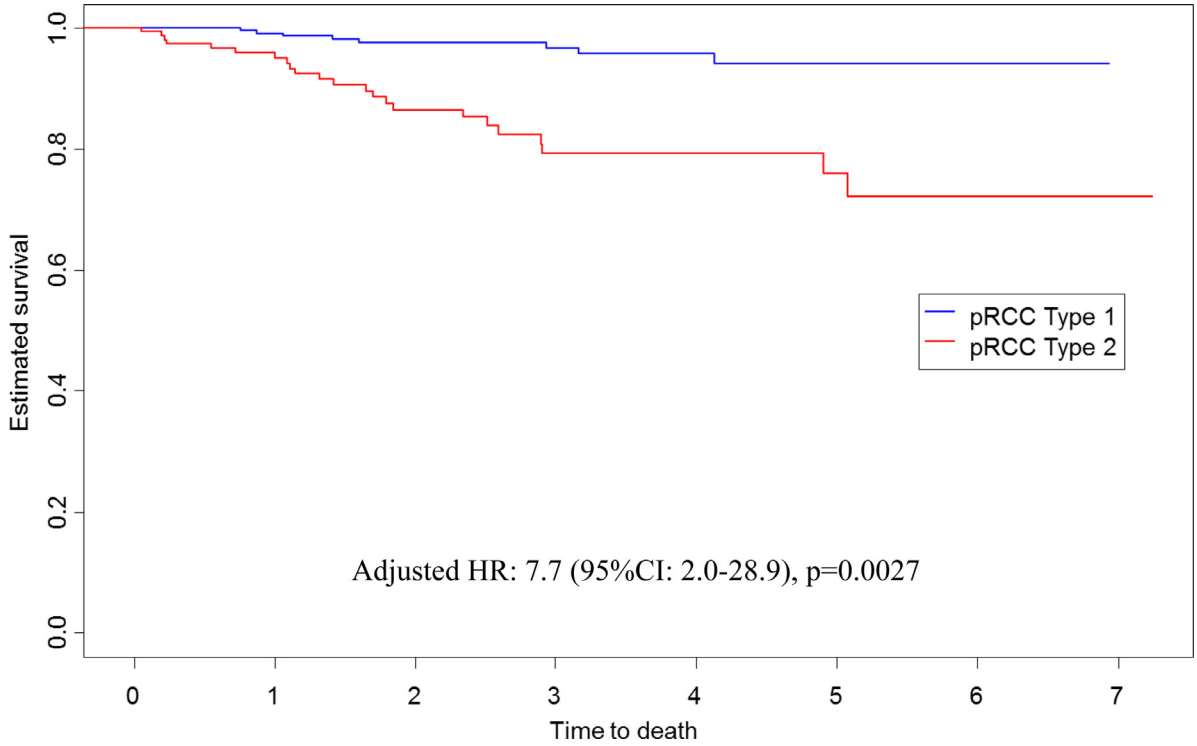

Fig. 2. Type 1 vs. type 2 pRCC in all-cause mortality.

profiling of the type 2 tumors revealed alterations of the CDKN2A/B, TERT, NF2, FH, and MET genes were prevalent, while alterations of the MET, TERT, CDKN2A/B, and EGFR genes were implicated in type 1 tumors [10]. While clinical outcomes were not compared, it is plausible that genetic differences between subtypes affect outcomes. As the study included a considerable number of patients with metastatic disease, it may be helpful in the design of future trials investigating therapies for advanced pRCC.

While the current study is valuable in providing validity to the need for pRCC subtyping, it can also help structure a framework on how clinical practice is dictated. Current practice guidelines do not discriminate between papillary subtyping for RCC follow-up. Our study supports the notion that reduced follow-up patterns can be implemented in patients with nonmetastatic type 1 pRCC. Moreover, when referring to our metastatic disease population, our data can help when assigning systemic therapy. Whereas the Canadian Urological Association guidelines only discriminate between clear cell renal cell carcinoma (ccRCC) and non-ccRCC, our study has shown that patients with metastatic type 2 pRCC have historic OS rates comparable to patients with metastatic ccRCC. A patient with type 1 pRCC, however, may only require surveillance with the possibility of delayed systemic therapy. As previously mentioned, given the molecular differences of pRCC and importance of subtyping, our study substantiates the need for a more diversified histopathology-based strategy in assigning targeted agents. The randomized phase II PAPMET trial, which included both type 1 and 2 pRCC indifferently, has started to take this approach [32]. The results of this study may also shed light on whether longer survival in type 1 pRCC reflects treatment effect or natural history.

Several limitations of our study should be noted. This study included patients receiving care at academic centers in Canada, which is a potential source of selection bias. In addition, central pathology review was not performed. Instead, the CKCis database relies on information found in pathology reports. Therefore, variance in reporting between pathologists from different centers was not assessed which is a potential source of bias. While this was a relatively large study, the impact of additional potential prognostic factors could not be assessed due to the limited number of recurrences, especially in patients with type 1 pRCC. Lastly, this study only included surgically treated patients. Patients treated with surveillance or thermal ablation were not included.

5. Conclusion

To the best of our knowledge, this is the largest study comparing pRCC subtypes. Our findings suggest that clinically localized type 2 pRCC is associated with unfavourable prognosis and higher metastatic potential compared to type 1 pRCC. Further attention to pRCC subtypes in the development and implementation of clinical practice and management guidelines is warranted on the basis of our study. Clinical trials should also likely stratify patients based on papillary subtype.

Conflicts of interest

None.

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