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Clinically localized type 1 and 2 papillary renal cell carcinomas have similar survival outcomes following surgery

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Abstract

Purpose We aimed to determine incidence, pathologic findings, prognostic factors and clinical outcomes for patients with clinically localized papillary RCC.

Methods Demographic, clinical and pathologic findings were collected on all patients with PRCC undergoing surgery at four academic medical centers. The primary endpoint was cancer-specific survival (CSS). Relapse-free survival (RFS) and overall survival (OS) were secondary endpoints. Kaplan–Meier estimates were obtained, and Cox proportional hazard regression models were used to assess predictors of mortality and relapse.

Results We identified 626 PRCC, of which 373 (60 %) were type 1 and 253 (40 %) were type 2, with three-quarters of all tumors being pT1. Compared to patients with type 1, those with type 2 were older (mean age: 63 vs 61; $p = 0.02$), presented more commonly with symptoms (13 vs 7 %; $p = 0.02$) and had larger mean tumor size (5.2 vs 4.3 cm; $p = 0.001$). With a median follow-up of 41 months (IQR: 16–68), 92 patients had died of PRCC (15 %), 48 (8 %) experienced relapse, and 101 died from all causes (16 %). The estimated 5-year CSS, RFS and OS were 83, 91 and 82 %, respectively. In multivariable analysis, older age, T stage and nodal status were predictors of CSS and OS. However, PRCC subtype was not a predictor of CSS, RFS or OS.

Conclusion While patients with type 2 PRCC appear to present with more advanced disease than patients with type 1, PRCC subtype does not appear to be an independent predictor of CSS, RFS or OS for treated localized disease.

Keywords Papillary RCC · Prognosis · Survival · Histological type

Abbreviations

PRCC	Papillary renal cell carcinoma
CSS	Cancer-specific survival
RFS	Relapse-free survival
OS	Overall survival
HR	Hazard ratio
SD	Standard deviation
CI	Confidence interval
IQR	Interquartile range

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Introduction

Papillary renal cell carcinoma (PRCC) is the second most frequent histologic type among all renal cortical neoplasms, accounting for up to 15 % [1]. Based on Delahunt and Eble's description, PRCC is morphologically subclassified

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into two groups, type 1 and type 2, depending on nuclear features and growth pattern characteristics [2, 3].

Since this subclassification was delineated, the aggressive potential of PRCC type 2 has been observed [4, 5], as patients with type 2 PRCC are diagnosed at a higher stage and harbor a higher nuclear grade compared to type 1 [6, 7]. Additionally, type 2 appears to be predominant in cases of PRCC with inferior vena cava thrombus [8] and has been reported to have lower cancer-specific survival compared to type 1 [5, 9].

Based on these findings, subclassification of PRCC has been suggested. However, there have been equivocal findings when the prognostic utility of PRCC subclassification has been assessed [5, 9–11].

Our aim was to evaluate a cohort of patients with clinically localized PRCC, to examine clinicopathologic factors, assess clinical outcomes and determine prognostic factors for recurrence and mortality.

Materials and methods

After obtaining institutional review board approval were retrospectively queried four institutional databases to identify patients with clinically localized PRCC (cT1-2 N0 M0) who underwent radical or partial nephrectomy between January 2002 and December 2012. The clinical information extracted included patient age, gender, symptoms at presentation, tumor size, operative data, pathologic findings and clinical follow-up.

All surgical procedures were performed by different surgeons using open or minimally invasive approaches. Lymph node dissection was performed when deemed necessary by preoperative imaging. RCC stage was assigned according to the American Joint Committee on Cancer 2010 TNM classification. A dedicated genitourinary pathologist re-reviewed each case and assigned histologic type following the recommendations of the Vancouver classification [12]. Patients with a history of synchronous or metachronous clear cell RCC were excluded from analysis. In addition, cases with mixed type 1 and type 2 or history of metachronous type 2 after type 1 PRCC were also excluded.

The patients were followed after surgery at regular intervals during visits to the outpatient clinic with history and physical examination. Radiographic surveillance imaging of the chest, abdomen and pelvis was obtained during different intervals according to each institution surveillance protocol. The length of the follow-up was considered the last information on file until the date of death.

The primary endpoint (PE) of the study was cancer-specific survival (CSS). This was defined as time from surgery to date of death from PRCC or last follow-up. The secondary endpoints were relapse-free survival (RFS) and overall survival (OS). Survival was determined from the respective institutional database, hospital records and the US Social Security Death Index. The evaluation of PE and SE was conducted using Kaplan–Meier estimates and the log-rank test. The impact of clinicopathological factors on mortality and recurrence was analyzed using Cox proportional hazard regression models, obtaining the HR and 95 % CI. Statistical analysis was conducted using Stata 12 (StataCorp, College Station, TX, USA).

Results

We identified 626 patients from the four institutions that underwent radical or partial nephrectomy between January 2002 and December 2012 and had PRCC at final pathology. After contemporary pathologic re-review, there were 373 (60 %) cases PRCC type 1 and 253 (40 %) type 2. There were 17 cases with mixed histology and therefore excluded from final analysis.

The clinical and pathological features according to PRCC subtype are given in Table 1. Mean age at surgery was 61 (SD = 12) for type 1 and 63 (SD = 12) for type 2 ($p = 0.02$). Patients with type 2 tumors presented with a larger tumor size [5.2 cm (SD = 4)] than patients with type 1 PRCC [4.3 cm (SD = 3), $p = 0.001$]. There were more males with type 1 PRCC (82 vs 72 %; $p = 0.004$). Patients with type 2 were more commonly symptomatic at presentation (13 vs 7 %; $p = 0.02$) and had higher incidence of vein thrombus (4 vs 0 %; $p = 0.001$). There were no differences with regard to surgical approach ($p = 0.5$).

Overall, 74 % of the tumors were pT1 and 84 % had organ-confined disease (pT2b or lower). There were no observable differences in the distribution according to T stage ($p = 0.8$). A lymph node dissection was undertaken in 98 patients (16 %), and in 21 % of the cases, a positive lymph node was detected (21/98). Type 2 patients were deemed for lymphadenectomy more commonly than type 1 (32 vs 11 %; $p < 0.001$) and were more likely to harbor lymph node metastasis (42 vs 9 %; $p = 0.01$).

At a median follow-up of 41 months (IQR: 16–68), 92 patients had died of PRCC (15 %), 48 with type 1 and 44 with type 2. A total of 48 (8 %) experienced relapse, and 101 died from all causes (16 %). The median time to recurrence was 45 and 32 months for type 1 and type 2, respectively. The estimated 5-year CSS was 83 % (95 % CI = 79–87). The estimated 5-year RFS was 91 % (95 % CI = 88–94), and the 5-year overall survival (OS) was 82 % (95 % CI = 78–86). There were 21 relapses in the type 1 group, the majority in the lungs (11/21). In type 2 patients, there were 27 relapses; most detected in the lung (16) or lymph nodes (10).
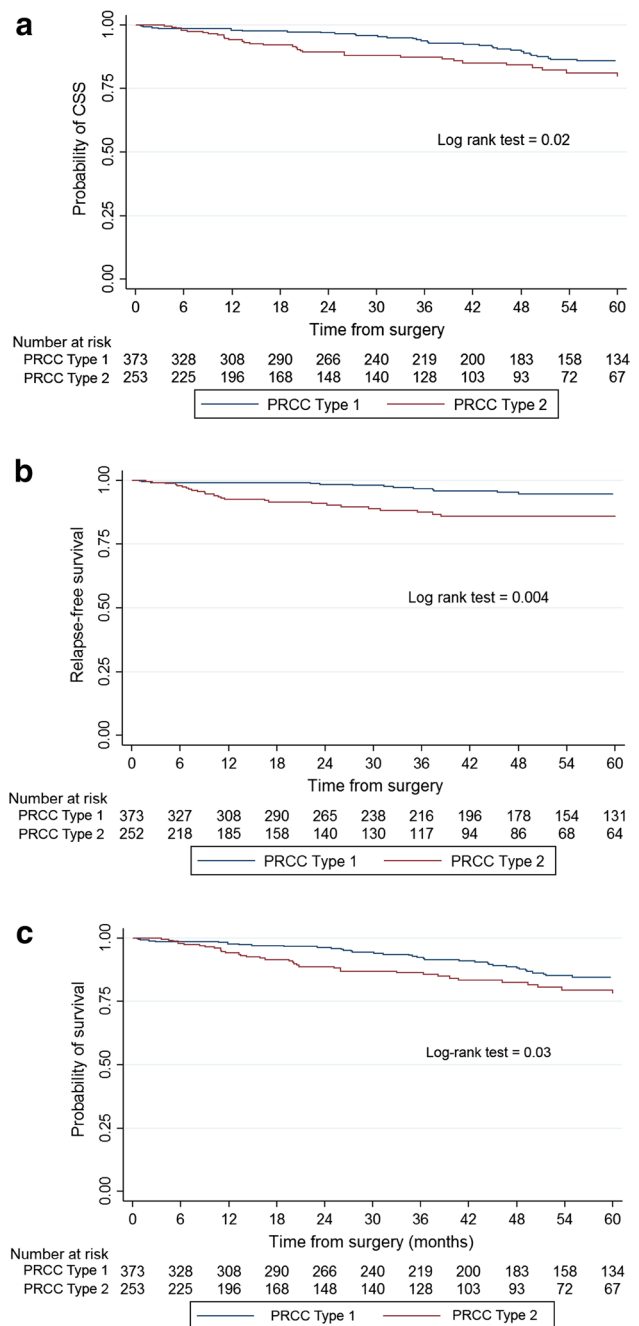
Table 1 Clinical, pathological and histological characteristics of 626 patients with papillary RCC

Characteristic	Type 1 = 373	Type 2 = 253	*p* value
Patients			
Mean age (SD)	61 (12)	63 (12)	**0.02**
Men (%)	306 (82 %)	183 (72 %)	**0.004**
Women (%)	67 (18 %)	70 (28 %)	**0.02**
Symptomatic at presentation	25 (7 %)	32 (13 %)	**<0.001**
Renal vein thrombus	0	10 (4 %)	
Treatment			
Radical nephrectomy	123 (33 %)	94 (37 %)	0.5
Partial nephrectomy	250 (67 %)	159 (63 %)	
Tumor size			
Mean (SD)	4.3 (3)	5.2 (4)	**0.001**
2010 Primary tumor classification			
pT1 (%)	288 (77)	175 (69)	0.8
pT1a	214	116	
pT1b	74	59	
pT2 (%)	34 (9)	29 (12)	
pT2a	18	20	
pT2b	16	9	
pT3 (%)	51 (14)	49 (19)	
pT3a	46	34	
pT3b	5	15	
2010 Regional lymph node (%)			
pNX	336 (90)	192 (76)	
pN0	34 (9)	43 (10)	
pN1	3 (0.8)	18 (7)	**<0.001**
Histologic features			
Multi-focal (%)	72 (19)	40 (16)	0.3
Sarcomatoid differentiation (%)	2 (0.5)	0	0.5
Necrosis (%)	13 (3.5)	11 (4.3)	0.7
Recurrence location			
Lymph node	3	10	
Lung	11	16	
Bone	1	2	
Kidney	6	4	
Other	2	3	

Bold values indicate statistical difference

Fig. 1 a Cancer-specific survival in papillary RCC stratified by type. **b** Relapse-free survival in papillary RCC stratified by type. **c** Overall survival in papillary RCC stratified by type

To evaluate the role of PRCC subtype in the prediction of recurrence and survival after surgical treatment, we compared the 5-year Kaplan–Meier CSS, RFS and OS (Fig. 1a–c) estimates by histologic subtype.

On univariable analysis, type 2 PRCC (HR = 1.7; 95 % CI = 1.1–2.5, *p* = 0.02), older age (HR = 1.07; 95 % CI = 1.04–1.09, *p* < 0.001), T stage (HR = 3.4; 95 % CI = 2–5, *p* < 0.001) and nodal status (HR = 7.6; 95 % CI = 4–14, *p* < 0.001) were predictors of CSS. With regard to relapse, type 2 PRCC (HR = 2.3; 95 % CI = 1.3–4, *p* = 0.005), T stage (HR = 3.5; 95 % CI = 2–6, *p* < 0.001) and nodal status (HR = 26; 95 % CI = 14–51, *p* < 0.001) were variables associated. Older age (HR = 1.07; 95 % CI = 1.05–1.09, *p* = 0.001), T stage (HR = 3; 95 % CI = 2.1–4.5, *p* = 0.001) and lymph node involvement (HR = 6.8; 95 % CI = 3.6–12, *p* = 0.001) were predictors of overall mortality (Table 2).

Table 2 Univariable and multivariable Cox regression analyses for prediction of cancer-specific survival (a), relapse-free survival (b) and overall survival (c) in surgically resected papillary RCC

Prognostic factor	Univariable			Multivariable		
	HR	95 % CI	p	HR	95 % CI	p
a						
Cancer-specific survival						
Age (years)	1.07	1.04–1.09	**<0.001**	1.05	1–1.07	**<0.001**
T stage						
pT1	1	ref	**<0.001**	1	ref	**<0.001**
pT2 and pT3	3.4	2.2–5.1		2.5	1.6–3.9	
N status						
N0 + NX	1	ref	**<0.001**	1	ref	**0.005**
N1	7.6	4–14		2.8	1.4–5.9	
Type						
1	1	ref	**0.02**	1	ref	0.4
2	1.7	1.1–2.5		1.2	0.8–1.9	
b						
Relapse-free survival						
Age (years)	1	0.9–1	0.9	0.9	0.9–1	0.4
T stage						
pT1	1	ref	**<0.001**	1	ref	**0.02**
pT2 and pT3	3.5	2–6.2		2.1	1.1–4	
N status						
N0 + NX	1	ref	**<0.001**	1	ref	**<0.001**
N1	26	14–51		15	6.8–35	
Type						
1	1	ref	**0.005**	1	ref	0.3
2	2.3	1.3–4		1.4	0.7–2.6	
c						
Overall survival						
Age (years)	1.07	1.05–1.09	**<0.001**	1.06	1–1.08	**<0.001**
T stage						
pT1	1	ref	**<0.001**	1	ref	**<0.001**
pT2 and pT3	3	2.1–4.5		2.2	1.5–3.4	
N status						
N0 + NX	1	ref	**<0.001**	1	ref	**0.009**
N1	6.8	3.6–12		2.6	1.3–5.4	
Type						
1	1	ref	**0.03**	1	ref	0.5
2	1.6	1.05–2.3		1.2	0.8–1.8	

Bold values indicate statistical difference

On multivariable analysis, T stage higher than pT1 (HR = 2.1; 95 % CI = 1.1–4, $p = 0.02$) and positive nodes (HR = 15; 95 % CI = 6.8–35, $p = 0.001$) were predictors of RFS. Age (HR = 1.05; 95 % CI = 1–1.07, $p < 0.001$), T stage (HR = 2.5; 95 % CI = 1.6–3.9, $p < 0.001$) and nodal involvement (HR = 2.8; 95 % CI = 1.4–6, $p = 0.005$) were independently associated with cancer-specific and overall mortality. PRCC subtype was not a predictor for CSS, RFS or OS in multivariable analyses (Table 2).

Discussion

We present a contemporary experience of surgically managed, clinically localized PRCC with the goal of better understanding differences in clinical outcomes as stratified by histologic subtype. Over the last few decades, there has been a rising incidence of renal cell carcinoma in the USA [13] with papillary being the second most common histologic subtype, accounting for approximately 13 % of all renal neoplasms [14].

PRCC generally has a favorable prognosis after surgical treatment [1, 14]; however, this entity represents a heterogeneous subset of patients with unique clinical characteristics [15]. Compared to patients with clear cell RCC, those with papillary histology are less likely to present with advanced stage and have a lower risk of cancer-specific and overall mortality [1, 14, 16].

The heterogeneity observed in outcomes of patients with PRCC is also seen at the histologic level, and two morphologically different groups have been postulated [2]. Type 1 is constituted by small cells with basophilic cytoplasm, and type 2 has larger cells with eosinophilic cytoplasm. This morphologic observation has been correlated with cytogenetic differences [3]. Jiang et al. [17] described that 7p and 17p gains are more commonly seen in type 1 than type 2. Moreover, this higher frequency of trisomy 17 present in type 1 has been associated with lower T stage, lower nodal involvement, less metastatic spread and longer survival [7]. Interestingly, unique features also have been delineated in type 2 PRCC, with a greater number of chromosomal aberrations than type 1 [17] (e.g., loss of 1p, loss of 3p and gain of 5q) [7].

The differing histologic and genetic features provide support to divide papillary RCC into two different entities, raising the question of variable recurrence and survival of PRCC based on histologic subtype.

Although patients with type 2 PRCC presented with larger tumors, were more likely to exhibit nodal disease and were more likely to harbor venous tumor thrombus, we did not find differences in CSS, OS and RFS probabilities between type 1 and type 2 PRCC on multivariate analyses. Previously, investigators have observed papillary type 2 as an independent predictor of cancer-specific mortality [5, 9]. However, this has not been reproduced by more contemporary series, suggesting subclassification of PRCC does not provide independent prognostic information at a given tumor stage [7, 10, 11].

The variability noticed across the PRCC literature may be due to the molecular biology of PRCC subtypes. Yang et al. [18] were able to identify subtle nuances by analyzing the differential gene expression profiles of 35 cases of PRCC. Using this methodology along with immunohistochemistry, they identified 2 different classes of PRCC. In class 1, three different histologic subtypes were aggregated: type 1, low-grade type 2 and mixed type 1/low-grade type 2. These patients had excellent survival, and their tumors had high expression of cytokeratin 7. The class 2 tumors were highly aggressive and characterized by having high-grade type 2 histology and expressing elevated levels of topoisomerase IIα. Clinically, they presented with higher rates of metastasis at surgery and poorer survival.

Aside from the underlying differences detected at the genetic level across the two different subtypes of PRCC, other factors play a role in predicting relapse and mortality. We identified stage and lymph node involvement as strong predictors of relapse in our multivariable model. This finding is in agreement with previous reports assessing factors related to recurrence and survival in PRCC. Margulis et al. [19] identified T stage, M status, presence of venous tumor thrombus and Fuhrman grade as independent predictors of disease-specific mortality by assessing 245 surgically treated PRCC. In a large multi-institutional experience summarized by Zucchi et al. [20], lymph node involvement, presence of metastases and Fuhrman grade were predictors of RFS and CSS. In order to provide further accuracy to the assessment of prognosis, a comprehensive nomogram has been proposed by Klatte et al. [21]. Incidental detection, TNM stage, vascular invasion and tumor necrosis were independent prognostic factors of DSS with an externally validated accuracy of 94 %. Consequently, the vast majority of the literature emphasizes the predominant role of TNM classification in determining the prognosis of a patient with PRCC.

The nuclear grading assessment of PRCC deserves special attention. This grading system was established before understanding that various types of RCC have distinctive clinical, genetic and histological features. Despite its widespread usage, there is debate regarding the reproducibility of its criteria and scant evidence to indicate that Fuhrman grading has prognostic utility for tumor types other than clear cell RCC [22]. Furthermore, it is unclear whether nucleolar grade alone or Fuhrman grade should be used in papillary RCC [23, 24]. A new grading system was recently proposed by the International Society of Urological Pathology, although further validation by confirmatory studies is warranted [25]. Based on the aforementioned reasons, we do not routinely quantify the Fuhrman grade in cases of PRCC at our institutions.

It has been previously suggested that PRCC has higher predilection for lymph node involvement [26, 27]. Compared to clear cell tumors, PRCC is more likely to have synchronous nodal metastases at the time of presentation [26], having a higher tendency to regional lymph node spread, especially in tumors measuring more than 8 cm [27]. In our cohort, we observed that 10 of 27 patients with papillary type 2 RCC who have a relapse exhibited metastatic disease in the lymph nodes, whereas most patients with type 1 PRCC metastasized to the lungs (11/21). This is consistent with data reported by Paparel et al. [28], who noted papillary type 2 accounts for up to 20 % of the surgically resected local recurrences. As such, it may be reasonable to obtain retroperitoneal imaging more frequently among patients with type 2 PRCC, in order to survey for nodal recurrences.

Our study has limitations that should be incorporated into the interpretation of our findings. We report a

multi-institutional retrospective experience in which four prospectively attained databases were queried to identify patients with PRCC. The inclusion and exclusion criteria were uniformly applied, and the output data were analyzed. Since not all databases were created with the exact same variables, we do not have the specific details regarding adjuvant treatment utilized in patients with T3 or N + disease. There may be patients with this high-risk feature who received some type of adjuvant treatment on a clinical trial. Nevertheless, the most common practice in the USA in these cases is to follow a close surveillance protocol since there are not drugs approved by the FDA to be utilized in the adjuvant setting. In addition, our study was not conceived to test different templates utilized when a retroperitoneal lymph node dissection was performed; therefore, we cannot provide more accurate data on template utilization in this setting. An additional drawback may be possible variations on surveillance imaging protocols utilized at the different institutions participating that could implicate differences in follow-up. Moreover, the patterns of care for postoperative relapse may have varied over the timeframe of our study, which may have influenced our study endpoints. It is also possible that longer follow-up would lead to different findings. However, our 1-, 3- and 5-year survivals are consistent with previous reports [1, 20].

In spite of its limitations, this study has the strength of being a multi-institutional experience of four academic centers representing a contemporary high-volume practice. In addition, we were able to gather what to our knowledge is the largest cohort of PRCC reported in the literature.

Conclusion

Patients with surgically treated type 2 PRCC present with larger tumor size, are more likely to exhibit synchronous nodal metastases and are more likely to harbor venous tumor thrombus than patients with type 1 PRCC. Nevertheless, when controlling for clinicopathological variables, PRCC subtype is not a predictor of CSS, RFS or OS. Type 2 PRCC more commonly recurs in regional lymph nodes.

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