Clinical and Pathological Features Associated With Prognosis in Patients With Papillary Renal Cell Carcinoma

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Abbreviations and Acronyms

PRCC = papillary RCC

RCC = renal cell carcinoma

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Purpose: We determined the clinical and pathological features associated with death from papillary renal cell carcinoma in 395 surgically treated patients.

Materials and Methods: Papillary renal cell carcinoma tissue slides from each patient were reviewed for type (1 or 2), grade, TNM stage, coagulative tumor necrosis and sarcomatoid differentiation. Associations of clinical and pathological features with death from renal cell carcinoma were evaluated using Cox proportional hazards regression models and summarized by the HR and 95% CI. Cancer specific survival was estimated using the Kaplan-Meier method.

Results: Univariate analysis revealed that symptoms, tumor thrombus, tumor size, perinephric/renal sinus fat invasion, 2010 primary tumor classification, regional lymph node involvement, distant metastasis, 2010 TNM stage group, grade, tumor necrosis, sarcomatoid differentiation and papillary renal cell carcinoma type were associated with death from renal cell carcinoma. Grade was more strongly associated with death from renal cell carcinoma than papillary renal cell carcinoma type. Multivariate analysis indicated that symptoms, 2010 TNM stage group and grade jointly were significantly associated with death from renal cell carcinoma.

Conclusions: This large series of patients with papillary renal cell carcinoma reveals features associated with death from renal cell carcinoma and confirms that grade is more predictive of outcome than papillary renal cell carcinoma type.

Key Words: kidney; carcinoma, renal cell; prognosis; mortality; neoplasms by histological type

Renal cell carcinoma consists of several histological subtypes with distinct morphological and genetic characteristics as well as dramatically different prognostic implications. PRCC is the second most common type of RCC, accounting for 10% to 15% of cases.[1,2] The most common classification system for PRCC divides these tumors into 2 distinct subtypes based on specific histological features, including type 1 or basophilic and type 2 or eosinophilic.[3] This system characterizes tumors composed of small round cells with basophilic nuclei and minimal cytoplasm that are distributed in a single cell layer on the surface of papillae as type 1 PRCC. These tumors are generally low grade with small nuclei and inconspicuous nucleoli, and are often associated with foamy macrophages. Type 2 tumors, which comprise less than a third of PRCCs, are characterized by eosinophilic cells with abundant cytoplasm and larger nuclei with

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prominent nucleoli arranged in a pseudostratified manner.[3]

Although many PRCCs can be readily classified as type 1 or 2, PRCC is commonly heterogeneous and can show type 1 and type 2 features, making classification difficult. In such situations groups have classified PRCC based on the predominant histological component while tumors with histological features of types 1 and 2 in relatively equal proportions have been classified as mixed.[4]

Patients with PRCC have a significantly better prognosis than those with clear cell RCC but some patients with PRCC die of metastatic disease.[1,2] Features predictive of outcome in patients with PRCC vary by study. For example, several studies indicate that type 2 PRCC is associated with a significantly worse prognosis than type 1.[3,4] However, this is not a consistent finding and issues related to PRCC tumor heterogeneity make it difficult to identify prognostic features.[5] Also, identifying prognostic features is further complicated by the lower frequency of PRCC relative to clear cell RCC and the few patients with PRCC who die of the disease. As a result, groups have used surrogate markers of tumor aggressiveness, including stage, grade and tumor size or overall survival, rather than cancer specific survival to evaluate prognostic features such as PRCC type.[3–5]

We investigated a large series of patients with PRCC to determine the prognostic value of various clinical and pathological features, including PRCC type. Our goal was to determine the most useful method of histological assessment to provide patients and clinicians with prognostic information.

MATERIALS AND METHODS

Patient Selection

Upon receiving institutional review board approval we identified 395 consecutive patients from the nephrectomy registry at our institution who were treated with radical nephrectomy or nephron sparing surgery for unilateral, sporadic PRCC between 1970 and 2002.

Clinical and Pathological Features

Clinical features studied included patient age, gender, symptoms and tumor thrombus. Patients with a palpable flank or abdominal mass, discomfort, gross hematuria, acute onset varicocele or constitutional symptoms, including rash, sweating, weight loss, fatigue, early satiety and anorexia, were considered symptomatic at presentation. Pathological features studied included perinephric/renal sinus fat invasion, 2010 primary tumor classification, regional lymph node involvement, distant metastasis, 2010 TNM stage group and unilateral multifocality, defined as more than 1 ipsilateral PRCC.

Histological features were assessed by a review of serial hematoxylin and eosin stained sections of nephrectomy specimens by a urological pathologist blinded to patient outcome. Histological features studied included grade, coagulative tumor necrosis and sarcomatoid differentiation. Grade was modified from Fuhrman grade and based only on nucleolar prominence other than grade 4.[1] Tumors with nucleoli readily visible at 100× magnification, filling at least 1 high power field, were classified as grade 3. Tumors with nucleoli visible at 200× magnification were considered grade 2. Tumors with inconspicuous nucleoli were classified as grade 1. Tumors were considered grade 4 if sarcomatoid differentiation was present or the lesion contained pleiomorphic or multinucleate cells.

Each lesion was also classified as type 1 or 2 based on the features used to describe PRCC in the original study by Delahunt and Eble.[3] Any tumor with type 2 areas was classified as type 2. In cases of multifocality the features of the largest lesion were studied.

Statistical Methods

Cancer specific survival was estimated using the Kaplan-Meier method. Followup was calculated from the date of surgery to the date of death or last known followup. Cause of death was determined from the death certificate or physician correspondence. Associations of clinical and pathological features with death from RCC were evaluated using Cox proportional hazards regression models and summarized with the HR and 95% CI. Statistical analysis was done with SAS®. All tests were 2 sided with $p < 0.05$ considered statistically significant.

RESULTS

Median age at surgery for the 395 study patients with PRCC was 65 years (range 25 to 89). The male-to-female ratio was 4.8 to 1. Table 1 lists the remaining clinical and pathological features studied. Of the 395 tumors 252 (64%) were classified as type 1 and 143 (36%) were classified as type 2 PRCC. A total of 26 type 1 PRCCs (10%) were multifocal compared to 8 type 2 PRCCs (6%) ($p = 0.11$).

At last followup 230 of the 395 patients studied had died, including 45 of PRCC a median of 2.8 years (range 0 to 16.5) after surgery. For the 165 patients who were alive at last followup median postoperative followup was 11.4 years (range 0.1 to 38.0). The estimated cancer specific survival rate 1, 5 and 10 years after surgery was 97.7% (95% CI 96.2–99.2) with 369 patients still at risk, 91.8% (95% CI 89.1–94.7) with 305 still at risk and 87.7% (95% CI 84.2–91.3) with 182 still at risk. Table 1 lists the clinical and pathological features of the 45 patients who died of RCC and the 350 who survived or died of another cause.

Univariate analysis revealed statistically significant associations of death from RCC with several clinical and pathological features (table 2). Patients with type 2 PRCC were significantly more likely to die of RCC than patients with type 1 PRCC (HR 2.16, 95% CI 1.20–3.89, $p = 0.010$). However, grade

Table 1. *Clinical, pathological and histological features of 395 patients*

	No. Pts (%)		No. Survived or Died of Other Cause (%)		No. Died of RCC (%)	
Age at surgery:						
Less than 65	178	(45)	155	(44)	23	(51)
65 or Greater	217	(55)	195	(56)	22	(49)
Gender:						
F	68	(17)	59	(17)	9	(20)
M	327	(83)	291	(83)	36	(80)
Symptoms at presentation:						
No	180	(46)	169	(48)	11	(24)
Yes	215	(54)	181	(51)	34	(76)
Constitutional symptoms at presentation:						
No	328	(83)	298	(85)	30	(67)
Yes	67	(17)	52	(15)	15	(33)
Tumor thrombus:						
None	380	(96)	344	(98)	36	(80)
Level 0	8	(2)	3	(1)	5	(11)
Level I–IV	7	(2)	3	(1)	4	(9)
Perinephric/renal sinus fat invasion:						
No	362	(91)	334	(95)	28	(62)
Yes	33	(8)	16	(5)	17	(38)
2010 Primary tumor classification:						
pT1a	184	(47)	180	(51)	4	(9)
pT1b	105	(27)	97	(28)	8	(18)
pT2a	40	(10)	34	(10)	6	(13)
pT2b	28	(7)	19	(5)	9	(20)
pT3a	28	(7)	16	(5)	12	(27)
pT3b	6	(2)	3	(1)	3	(7)
pT3c	1	(less than 1)	0		1	(2)
pT4	3	(1)	1	(less than 1)	2	(4)
2010 Regional lymph node involvement:						
pNX + pN0	376	(95)	343	(98)	33	(73)
pN1	19	(5)	7	(2)	12	(27)
Distant metastasis:						
M0	381	(96)	347	(99)	34	(76)
M1	14	(4)	3	(1)	11	(24)
2010 TNM stage group:						
I	284	(72)	275	(79)	9	(20)
II	62	(16)	51	(15)	11	(24)
III	34	(9)	21	(6)	13	(29)
IV	15	(4)	3	(1)	12	(27)
Multifocality:						
No	361	(91)	320	(91)	41	(91)
Yes	34	(9)	30	(9)	4	(9)
Grade:						
1	8	(2)	8	(2)	0	
2	239	(61)	224	(64)	15	(33)
3	143	(36)	117	(33)	26	(58)
4	5	(1)	1	(less than 1)	4	(9)
Coagulative tumor necrosis:						
No	209	(53)	191	(55)	18	(40)
Yes	186	(47)	159	(45)	27	(60)
Sarcomatoid differentiation:						
No	391	(99)	349	(100)	42	(93)
Yes	4	(1)	1	(less than 1)	3	(7)
Type:						
1 (basophilic)	252	(64)	230	(66)	22	(49)
2 (eosinophilic)	143	(36)	120	(34)	23	(51)

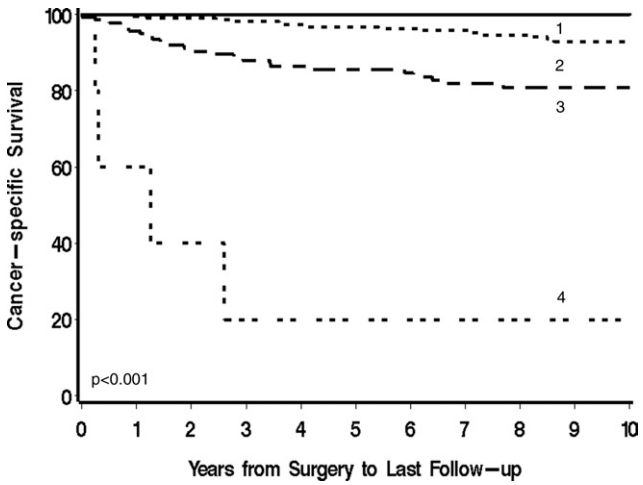
was an even stronger predictor of death from RCC (HR 3.97, 95% CI 2.14–7.39, p <0.001, see figure). For grade 1 PRCC the cancer specific survival rate 1, 5 and 10 years after surgery was 100% (95% CI 100–100) with 8 patients still at risk, 100% (95% CI 100–100) with 7 at risk and 100% (95% CI 100–100) with 6 at risk, respectively. For grade 2 the rate was 99.6% (95% CI 98.7–100) with 229 patients still at risk, 96.8% (95% CI 94.5–99.2) with 197 at risk and 92.8% (95% CI 89.1–96.5) with 117 at risk, respectively. For

Table 2. *Univariate associations with death from RCC in 395 patients*

	HR (95% CI)	p Value
Age at surgery:		
Less than 65	1.0 (referent)	
65 or Greater	0.90 (0.50–1.62)	0.72
Gender:		
F	1.0 (referent)	
M	0.89 (0.43–1.85)	0.76
Symptoms at presentation:		
No	1.0 (referent)	
Yes	2.66 (1.35–5.26)	0.005
Constitutional symptoms at presentation:		
No	1.0 (referent)	
Yes	2.75 (1.48–5.12)	0.001
Tumor thrombus:		
None	1.0 (referent)	
Level 0–IV	12.94 (6.16–27.19)	<0.001
Perinephric/renal sinus fat invasion:		
No	1.0 (referent)	
Yes	11.60 (6.25–21.50)	<0.001
2010 Primary tumor classification:		
pT1a, pT1b, pT2a + pT2b	1.0 (referent)	
pT3a, pT3b, pT3c + pT4	9.69 (5.30–17.73)	<0.001
2010 Regional lymph node involvement:		
pNX + pN0	1.0 (referent)	
pN1	17.68 (8.93–34.99)	<0.001
Distant metastasis:		
M0	1.0 (referent)	
M1	20.99 (10.47–42.05)	<0.001
2010 TNM stage group:		
I + II	1.0 (referent)	
III + IV	15.65 (8.58–28.54)	<0.001
Multifocality:		
No	1.0 (referent)	
Yes	1.04 (0.37–2.91)	0.94
Grade:		
1 + 2	1.0 (referent)	
3 + 4	3.97 (2.14–7.39)	<0.001
Coagulative tumor necrosis:		
No	1.0 (referent)	
Yes	1.86 (1.03–3.38)	0.041
Sarcomatoid differentiation:		
No	1.0 (referent)	
Yes	13.33 (4.10–43.38)	<0.001
Type:		
1 (basophilic)	1.0 (referent)	
2 (eosinophilic)	2.16 (1.20–3.89)	0.010

grade 3 the rate was 95.7% (95% 92.3–99.1) with 129 patients still at risk, 85.6% (95% 79.7–91.8) with 100 at risk and 80.8% (95% 74.1–88.1) with 58 at risk, respectively. For grade 4 the rate was 60.0% (95% 29.3–100) with 3 patients still at risk, 20.0% (95% 3.5–100) with 1 at risk and 20.0% (95% 3.5–100) with 1 at risk, respectively.

Multivariate analysis indicated that symptoms at presentation, 2010 TNM stage group and grade jointly were significantly associated with death from PRCC (table 3). After adjusting for these features patients with type 2 PRCC were no more likely to die from RCC than those with type 1 (HR 0.86, 95% CI 0.44–1.69, p = 0.66).



Cancer specific survival by grade for 395 patients with PRCC (p <0.001).

When analysis was restricted to pT1 and pT2 disease, there remained a significant difference in outcome with a significantly better cancer specific outcome for pT1 than for pT2 tumors (pT2 vs pT1 HR 5.95, 95% CI 2.78–12.73, p <0.001). Finally, when analysis excluded the 5 grade 4 tumors and focused on lesions assessed only by nucleolar size, grade remained a stronger predictor of death from PRCC than type (grade 3 vs 1 and 2 HR 3.54, 95% CI 1.87–6.69, p <0.001). In this setting a multivariate model would continue to include symptoms at presentation, TNM stage and grade.

DISCUSSION

PRCC has long been recognized as a distinct RCC subtype. Recent large studies showed that PRCC has a significantly better outcome than clear cell RCC but the prognostic features of PRCC are not well defined.[1,2] Several clinical and pathological features were identified as having a significant association with outcome, including tumor stage, grade and PRCC type. However, although tumor stage is

Table 3. *Multivariate associations with death from RCC in 395 patients*

	HR (95% CI)	p Value
Symptoms at presentation:		
No	1.0 (referent)	
Yes	2.43 (1.22–4.81)	0.011
2010 TNM stage groups:		
I + II	1.0 (referent)	
III + IV	13.33 (7.16–24.80)	<0.001
Grade:		
1 + 2	1.0 (referent)	
3 + 4	2.82 (1.49–5.32)	0.001

consistently prognostic, grade and PRCC type are not. Studies have been limited by sample size, the infrequency of death related to RCC and the use of death from any cause or surrogate markers of aggressiveness as the end point rather than cancer specific death. We evaluated the features of a large PRCC series, including type, to identify prognostic features using cancer specific death as the end point.

In 1997 Delahunt and Eble proposed a histological classification of PRCC into 2 morphologically distinct types based on specific cytological and architectural features.[3] In their original description type 1 PRCC is composed of small cells with small oval nuclei, and with inconspicuous nucleoli and pale cytoplasm lining papillary structures and tubules. They identified foamy macrophage infiltration of papillary cores and psammoma bodies as common features of type 1 lesions. In contrast, type 2 PRCC is composed of large cells with abundant eosinophilic cytoplasm and large round nuclei with prominent nucleoli growing in a pseudostratified arrangement on papillae. Foamy macrophages and psammoma bodies are rare findings in these tumors. In the original study of 100 patients PRCC type was significantly associated with tumor size, stage and grade but no correlation with outcome was determined.

In the subsequent study of 66 patients by Delahunt et al PRCC type was not associated with TNM stage or tumor size but it was associated with overall patient survival.[6] In that series 16 patients had type 2 tumors, of whom 8 died, and 50 had type 1 tumors, of whom 19 died. Cause of death was not provided. Subsequently Pignot et al studied 130 patients with PRCC and identified on multivariate analysis that PRCC type and TNM stage were significantly associated with cancer specific survival.[4] A study of 103 patients by Tickoo and Reuter showed that PRCC type was not significantly associated with outcome.[5]

The original description thoroughly detailed the histological features characteristic of PRCC types 1 and 2, readily allowing a PRCC classification conforming to the type 1 or 2 description. However, PRCC is heterogeneous and can show features characteristic of types 1 and 2. Allory et al found that 35% of PRCC in their series had overlapping features.[7] The original description of PRCC type did not address the heterogeneity that may be seen in these tumors. Subsequently groups have used variable criteria to designate PRCC or attempted to rectify this dilemma by classifying PRCC into a third category of mixed PRCC. Thus, we systematically studied clinical and pathological features, including a standardized assessment of type and grade, in a series of 395 patients with PRCC to determine which features have prognostic implications.

In our analysis we identified that symptoms at presentation, renal vein tumor thrombus, perinephric/renal sinus fat involvement, advanced 2010 TNM stage group, high grade, coagulative tumor necrosis, sarcomatoid differentiation and PRCC type were univariately associated with an increased risk of death from RCC. The significance of symptoms, TNM stage group and grade were maintained on multivariate analysis.

Grade was more strongly associated with outcome than PRCC type. Our findings are in agreement with a study of 90 cases by Sika-Paotonu et al demonstrating that nucleolar grade is significantly associated with outcome in patients with PRCC.[8] They found that on multivariate analysis nucleolar grade was significantly associated with outcome but PRCC type was not. The grading system used in our study relied on focal nucleolar prominence for grades 1 to 3 and for nuclear size or a sarcomatoid component for grade 4. When we analyzed the data set after excluding grade 4 tumors and assessed it only by nucleolar size, grade remained a stronger predictor of outcome than PRCC type. Although nucleolar size is a prominent component of the Fuhrman grading system, nuclear size and shape are components, most notably for grade 4 tumors.

The best method to assess PRCC grade has been a point of controversy.[8–10] As in practice, in the current study we applied a grading system based only on nucleolar prominence for tumors assessed as grade 1 to 3, that is grade 3 has readily visible nucleoli at 100× magnification while grades 1 and 2 do not. For grade 4 tumors nuclear size and shape are included in the assessment. The grading system that we use is a modification of the Fuhrman grading system. In our practice there is a strong concordance of the Fuhrman grading system and grade based on the visibility of nucleoli at various magnifications. This system is used by many pathologists to grade clear cell and papillary RCC.[11] In our experience this system is significantly associated with cancer specific outcome for clear cell RCC and PRCC on univariate and multivariate analysis.

Our findings of the significant association of coagulative tumor necrosis with patient outcome contrast with our previous report.[1] Previously we could not identify a significant relationship between tumor necrosis and prognosis while in our study this tumor feature achieved statistical significance ($p = 0.041$). An explanation of this discrepancy may be that including more tumors with longer followup and, thus, more deaths from RCC may have uncovered significance that was not detectable in our previous smaller series. We also identified a significant

difference in outcome between pT1 and pT2 tumors and the fact that the current TNM staging system for confined tumors is relevant for PRCC.

CONCLUSIONS

Our findings indicate that several features are significantly associated with outcome in patients with PRCC treated surgically, including symptoms at presentation, 2010 TNM stage group and grade. Thus, proper clinical and pathological classification of PRCC should include assessment of these specific features. However, histological classification as type 1 or 2 was not associated with outcome in a multivariate setting. Future study will require consensus agreement on a grading system for PRCC. Lastly, there is need for a greater understanding of the tumor heterogeneity of PRCC to determine whether it is a reflection of a dedifferentiation pathway or PRCC represents a heterogeneous group of tumors requiring further refinement at the histological and molecular levels.

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