

Clinicopathological Features of Papillary Renal Cell Carcinoma With Venous Tumor Thrombus: Case Series from a Large Chinese Center

Clinical Medicine Insights: Oncology
Volume 16: 1–9
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/11795549221092217



Zhuo Liu^{1†}, Liyuan Ge^{1†}, Xun Zhao¹, Min Lu², Abudureyimujiang Aili³, Yuxuan Li¹, Guodong Zhu¹, Peng Hong¹, Xiaojun Tian¹, Shumin Wang⁴, Hongxian Zhang¹, Cheng Liu¹, Zhenshan Ding⁵, Shudong Zhang¹ and Lulin Ma¹

¹Department of Urology, Peking University Third Hospital, Beijing, P.R. China. ²Department of Pathology, School of Basic Medical Sciences, Peking University Third Hospital, Peking University Health Science Center, Beijing, P.R. China. ³Department of Radiation Oncology, Peking University Third Hospital, Beijing, P.R. China. ⁴Department of Ultrasound, Peking University Third Hospital, Beijing, P.R. China. ⁵Department of Urology, China-Japan Friendship Hospital, Beijing, P.R. China. ⁶Peking University Third Hospital, Beijing, P.R. China.

ABSTRACT

BACKGROUND: Few studies have reported the influence of the histological classification of type-2 papillary renal cell carcinoma (PRCC), which may differ from that of clear cell renal carcinoma (ccRCC), on the prognosis of renal cell carcinoma with tumor thrombus. We investigated the clinicopathological features and prognosis of type-2 PRCC associated with venous tumor thrombi (PRCC-TT).

METHODS: We retrospectively analyzed 163 patients with renal cell carcinoma with venous tumor thrombus (RCC-TT) admitted to Peking University Third Hospital between June 2016 and June 2020. Twenty-five patients had type-2 PRCC-TT and 138 had ccRCC combined with tumor thrombus; there were 125 males and 38 females. All the included patients underwent radical nephrectomy and thrombectomy under either complete laparoscopic surgery or open surgery. Univariate and multivariate Cox regression analysis were performed to evaluate the prognostic significance of each variable on cancer-specific survival (CSS). Cancer-specific survival was calculated from the date of surgery to death or the last follow-up using the Kaplan–Meier method.

RESULTS: The blood vessels of type-2 PRCC-TT presented on CT images were not as abundant as those of ccRCC-TT. Slight enhancement was observed in the corticomedullary phase. While wash-out symptoms were observed, contrast agent extinction was not obvious in the nephrographic and excretory phases. We compared the macroscopic and microscopic appearances of the 2 cohorts. Compared to the ccRCC-TT cohort, lymph node invasion was more prevalent in the PRCC-TT cohort (88.0% vs. 60.9%, $P = .009$). Multivariate analysis revealed that sarcomatoid differentiation, distant metastasis, and pathological type were the independent predictors of poor CSS. The Kaplan–Meier analysis showed that the CSS of type-2 PRCC-TT and ccRCC-TT were 23.5 and 38.4 months, respectively, with statistical significance ($P = .002$).

CONCLUSION: Type-2 PRCC-TT varies with common ccRCC-TT in imaging manifestation and pathological characteristics. The prognosis of type-2 PRCC-TT patients was worse than that of ccRCC-TT patients.

KEYWORDS: Clinicopathological features, inferior vena cava, papillary renal cell carcinoma, clear cell renal cell carcinoma, tumor thrombus

RECEIVED: December 10, 2021. **ACCEPTED:** March 18, 2022.

TYPE: Original Research Article

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Nature Science Foundation of China (grant no. 81771842).

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHORS: Lulin Ma, Department of Urology, Peking University Third Hospital, 49 North Garden Road, Haidian, Beijing 100191, P.R. China. Email: malulinpku@163.com

Shudong Zhang, Department of Urology, Peking University Third Hospital, 49 North Garden Road, Haidian, Beijing 100191, P.R. China. Email: shootong@163.com

Introduction

Papillary renal cell carcinoma (PRCC) is a distinct pathological subtype of renal cell carcinoma (RCC). It is the second most common subtype of renal carcinoma after clear cell renal carcinoma (ccRCC), accounting for approximately 15% to 20% of all RCC cases.¹ Mancilla-Jimenez et al² first described and defined the clinical, radiologic, and pathologic features of PRCC in

1976. Papillary renal cell carcinoma originates from the epithelial cells of the proximal and distal tubules of the renal cortex and grows in a papillary pattern. Tumor tissue often forms tubules and papillary structures, and the axis of the papillary structure is fibrovascular tissue. Papillary renal cell carcinoma can be classified into 2 subtypes according to cell and structural characteristics. Among them, type-2 PRCC is covered with pseudostratified epithelium, large tumor cells, eosinophilic cytoplasm, obvious nucleoli, rare calcification, and foam macrophages along the axis

[†]These authors contributed equally to this work.



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

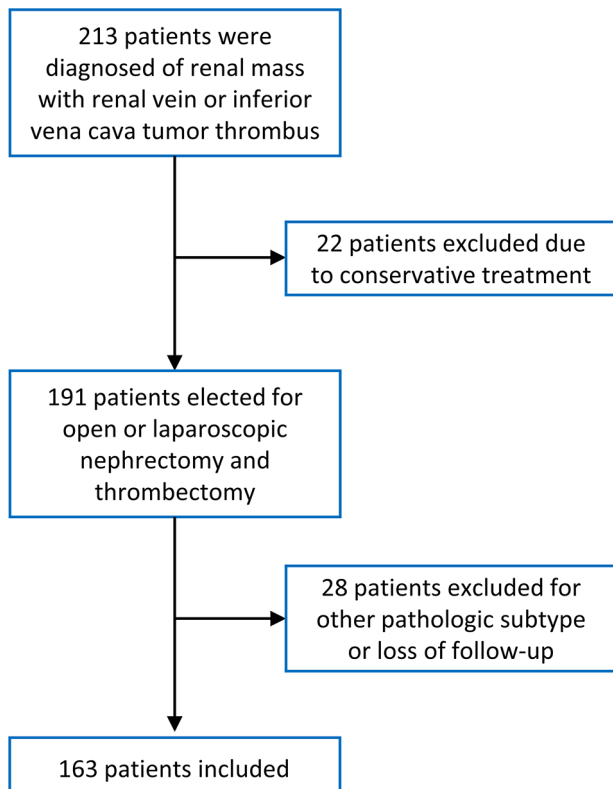


Figure 1. The standard flow chart of inclusion criteria.

of the papillary structure. Compared with type-1 PRCC, type-2 PRCC is more malignant, and its prognosis is even worse.³

One of the characteristics of RCC is its propensity to invade the venous system, extending into the renal vein or inferior vena cava. Meanwhile, most current studies examine RCC as a whole or focus on mainly ccRCC.^{4,5} Few studies have reported the influence of histological classification on the prognosis of RCC with tumor thrombus. The prognosis of type-2 PRCC may be worse than that of ccRCC with a tumor thrombus.^{6,7} To explore the clinicopathological features and prognosis of type-2 PRCC with venous tumor thrombus, we retrospectively analyzed the data of 163 cases of RCC with renal vein or inferior vena cava tumor thrombus.

Materials and Methods

Basic information

We retrospectively analyzed the data of 163 patients diagnosed with RCC with venous tumor thrombus who had been treated with radical nephrectomy and thrombectomy at Peking University Third Hospital from June 2016 to June 2020. The inclusion criteria were as follows: (1) involvement of a renal tumor in patients with renal vein or inferior vena cava as suggested by imaging and (2) postoperative pathological confirmation of type-2 PRCC or ccRCC. The exclusion criteria are as follows: postoperative pathological diagnoses include other subtypes, such as oncocytoma, Ewing sarcoma, and squamous cell carcinoma. A flowchart of the inclusion criteria is shown in Figure 1.

Radiological and anatomic-pathological characteristics of the type-2 papillary RCC compared to the ccRCC

According to the clinical symptoms, patients were divided into asymptomatic patients, those with local symptoms (such as low back pain, hematuria, and abdominal mass), those with general symptoms (such as fatigue, fever, and weight loss), and those with both local and general symptoms. Before surgery, urinary system-enhanced computed tomography (CT) and/or inferior vena cava-enhanced magnetic resonance imaging (MRI) were performed to evaluate the side, diameter, location, and morphological characteristics of renal tumors, presence or absence of lymph node metastasis, and thrombus length. In the nephrographic phase of urinary system-enhanced CT, the contrast agent exited in the parenchymal phase, but the exit range was slight in type-2 PRCC-TT. However, the contrast agent exited in the parenchymal phase, and the exit range was large in ccRCC-TT. In microscopic cellular morphology, the cells are alkaline or chromotropic, show papillary or tubular papillary growth, and the axis is rich in lipid-containing foam-like macrophages in type-2 PRCC-TT. However, the cells were round or polygonal, rich in cytoplasm, contained a large amount of glycogen and phospholipids, and dissolved by solute in the process of tableting showing a transparent shape in ccRCC-TT.

All the patients underwent either complete laparoscopic surgery or open surgery. We have introduced the position and steps of the laparoscopic and open approaches in the literature.⁸ Different surgical strategies have been developed according to the Mayo classification of tumor thrombus.⁹⁻¹¹

Statistical method and prognostic factors

Continuous variables with a normal distribution are shown as mean \pm standard deviation, and categorical variables are summarized as percentages. For comparison of continuous variables, student's *t*-test was used, and chi-square tests were used to compare categorical variables. Cox proportional hazard models were used for univariate and multivariate analyses. The Kaplan-Meier curve was used to evaluate the influence of pathological type on cancer-specific survival (CSS). All statistical analyses were performed using SPSS version 18.0. Statistical significance was set at $P < .05$.

Results

Baseline results

There were 25 and 138 cases of type-2 PRCC and ccRCC, respectively. Among 163 patients, there were 125 men and 38 women. Their ages ranged from 31 to 83 years with an average of 59.9 years. The body mass index (BMI) ranged from 15.2 to 39.0 kg/m² with an average of 23.8 kg/m². Renal tumors were located on the right side in 103 patients and on the left side in 60 patients. The American Association of Anesthesiologists (ASA) scoring system was used to evaluate the risks of surgery

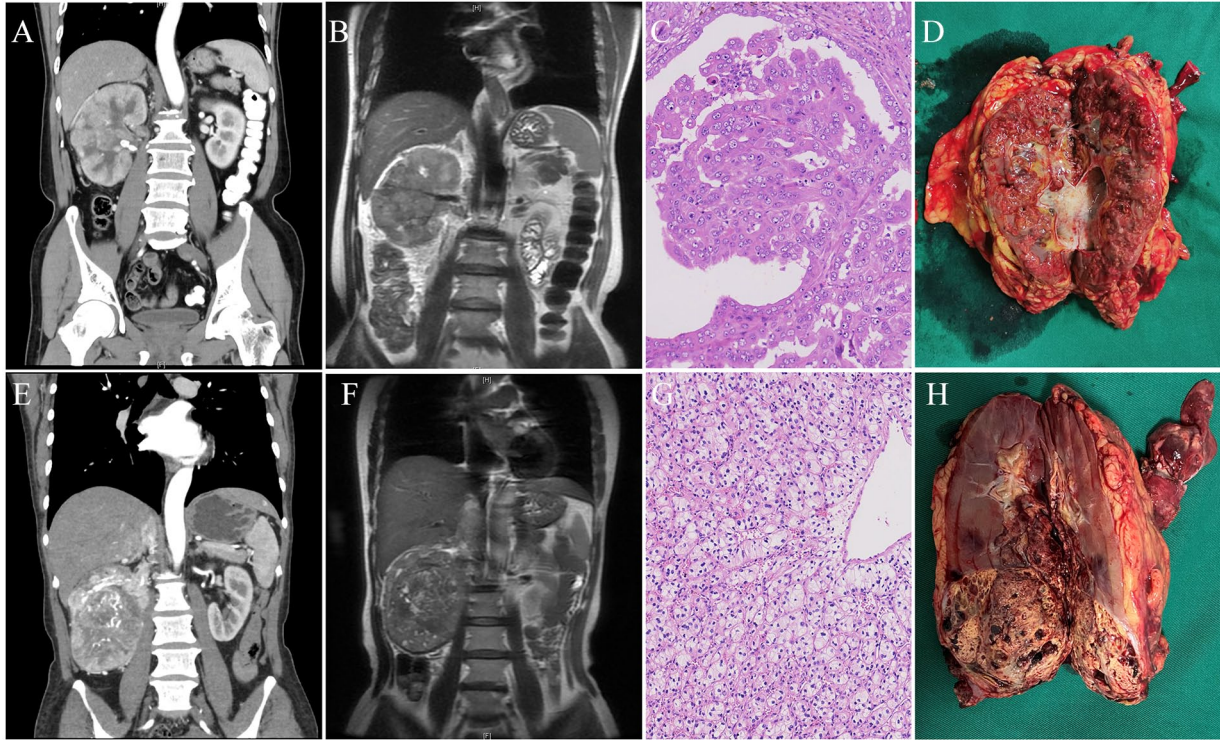


Figure 2. Typical imaging pictures, gross specimen pictures, and HE staining pictures of type-2 PRCC-TT and ccRCC-TT: (A) typical enhanced CT images of type-2 PRCC-TT; (B) typical enhanced MRI findings of type-2 PRCC-TT; (C) pathological HE staining picture of type-2 PRCC-TT; (D) typical picture of type-2 PRCC-TT specimen; (E) typical enhanced CT findings of ccRCC-TT; (F) typical enhanced MRI findings of ccRCC-TT; (G) typical picture of PRCC-TT gross specimen PRCC-TT; and (H) pathological HE staining picture of ccRCC-TT.

and anesthesia. The ASA was classified as grade 1 in 7 cases, grade 2 in 137 cases, and grade 3 in 19 cases.

Radiological results

Among 163 cases of RCC associated with venous tumor thrombus, 25 were type-2 PRCCs. By reviewing the imaging data in this study, we found that the blood supply of type-2 PRCC was less abundant than that of ccRCC; therefore, it had a unique manifestation in CT and MRI images. Clear cell renal carcinoma had more abundant blood vessels, and obvious enhancement in the renal cortex phase was observed in the corticomedullary phase. As shown in Figure 2, neovascular characteristics, lack of normal vascular structure, uneven blood vessel density, existence of an arteriovenous short circuit, and abnormal hemodynamics lead to uneven enhancement in CT or MR images. For the same reason, “fast forward and fast rewind” signs were observed during the delay period (Figure 2). However, the vessels of type-2 PRCCs were less abundant than those of ccRCCs. Although enhancement in the cortical phase was observed, the degree of enhancement was low. Furthermore, a slight withdrawal of the contrast medium was also observed in the nephrographic and excretory phases. These imaging findings are helpful for clinicians in making preoperative diagnoses and determining the appropriate treatment.

Anatomo-pathological results

Regarding the appearance of gross specimens, the tumor section of type-2 PRCC is beige and rich in oil, which may be accompanied by hemorrhage, necrosis, and cystic change. The tumor section of ccRCC is mainly yellow, which may be accompanied by gray or white lesions, most of which are solid and a few are cystic. The cells of type-2 PRCC were alkaline or chromotropic, and the cells showed papillary or tubular papillary growth patterns with lipid-containing foam-like macrophages in the axis, as shown in Figure 2. However, the cells of ccRCC were round or polygonal with abundant cytoplasm that contained a large amount of glycogen and phospholipids, which are dissolved by solutes in the production process and were transparent. The imaging and pathological features, and differences between the 2 pathological types are shown in Table 1.

Prognostic results

As shown in Table 2, lymph node invasion was more prevalent in patients with type-2 PRCC than in those with ccRCC (88% vs. 60.9%, $P=.009$). There were no significant differences between the 2 cohorts in terms of sex, age, BMI, side, ASA score, clinical symptoms, distant metastasis, Mayo grade, preoperative serum creatinine level, tumor diameter, surgical approach, intraoperative segmental resection of the inferior

Table 1. Different imaging and pathological manifestations of type-2 papillary renal cell carcinoma with venous tumor thrombus and clear cell renal cell carcinoma with venous tumor thrombus.

	SPECIFIC INDICATORS	TYPE-2 PRCC-TT	CCRCC-TT
Urinary system enhanced CT	Corticomedullary phase	There was enhancement in cortical stage, but the degree of enhancement was low	There is enhancement in corticomedullary phase, and the degree of enhancement is high (cause: blood vessels are abundant). Uneven enhancement (causes: lack of normal blood vessels in neovascularization, uneven distribution of blood vessel density, short circuit between arteries and veins, and abnormal hemodynamics of neovascularization)
	Nephrographic phase	The contrast agent exited in the parenchymal phase, but the exit range was slight	The contrast agent exited in the parenchymal phase, and the exit range was large
Enhanced MRI of inferior vena cava	Plain scanning phase	Bleeding and cystic changes are common	Bleeding, necrosis, neovascularization, and cystic change can be seen
	Enhancement phase	The enhancement index in cortical, parenchymal, and delayed stages was lower, and gradually increased slightly from cortical to parenchymal stage, while the signal from parenchymal to delayed stage decreased	The enhancement index of cortical stage, parenchymal stage, and delayed stage is high, showing a gradual decline, showing a “fast forward and fast rewind” enhancement mode
	T1WI	Clutter	Most of them are mixed signals, and a few are low signals
	T2WI	Clutter	Most of them are mixed signals, and a few are high signals
Gross performance	Renal tumor shape	Irregular or round lobulated mass with unclear boundary	Most of them are round, and when the tumor is large, it can be nodular or lobulated
	Renal tumor section	It is beige and rich in oil, and may be accompanied by hemorrhage, necrosis, and cystic change	Mainly yellow, may be accompanied by gray or white lesions, mostly solid, a few cystic
Microscopic morphology	Cellular morphology	The cells are alkaline or chromotropic, and the cells show papillary or tubular papillary growth, and the axis is rich in lipid-containing foam-like macrophages	Round or polygonal, rich in cytoplasm, containing a large number of glycogen, phospholipids, etc., dissolved by solute in the process of tableting, showing a transparent shape
	Nucleolar expression	The nucleus is enlarged and the nucleolus is obvious	The nucleus contracted and chromatin increased and stained intensively. Nuclear diversity, obvious nucleolus

vena cava, surgical time, sarcomatoid differentiation, and post-operative serum creatinine. Univariate analysis showed that lymph node metastasis, sarcomatoid differentiation, distant metastasis, and pathological subtype were the risk factors for CSS. Multivariate analysis showed that only sarcomatoid differentiation, distant metastasis, and pathological subtype were independent risk factors for CSS (Table 3). The survival analysis showed that the CSS rates of type-2 PRCC-TT and ccRCC-TT were 23.5 and 38.4 months, respectively ($P=.002$) (Figure 3). Therefore, the prognosis of type-2 PRCC with venous tumor thrombus is worse than that of clear cell carcinoma with venous tumor thrombus.

Discussion

Papillary renal cell carcinoma originates from the epithelial cells of the proximal and distal tubules of the renal cortex and grows in a papillary pattern. Tumor tissue often forms tubules and

papillary structures, and the axis of the papillary structure is fibrovascular tissue. Papillary renal cell carcinomas can be classified into type-1 and type-2 according to the cell and structural characteristics.¹² In our center, the pathological diagnosis of PRCC was differentiated mainly by histological morphology and immunohistochemical (IHC) histology. Regarding histological morphology, the tumor cells of type-2 papillary cell carcinoma are covered with pseudostratified columnar epithelial cells, whereas type-1 PRCC is covered by monolayer cubic small cells. Moreover, compared with type-1 PRCC, the cancer cells of type-2 PRCC are larger with a large nucleus and sarcomatoid differentiation. Regarding IHC features, type-1 PRCC is accompanied by high expression of CK7 and Epithelial membrane antigen (EMA), which have low expression in type-2 PRCC. Among them, type-2 PRCC is covered with pseudostratified epithelium with large tumor cells, eosinophilic cytoplasm, obvious nucleoli, rare calcification, and foam

Table 2. Comparison of clinical and pathological characteristics between type-2 papillary renal cell carcinoma and clear cell renal cell carcinoma.

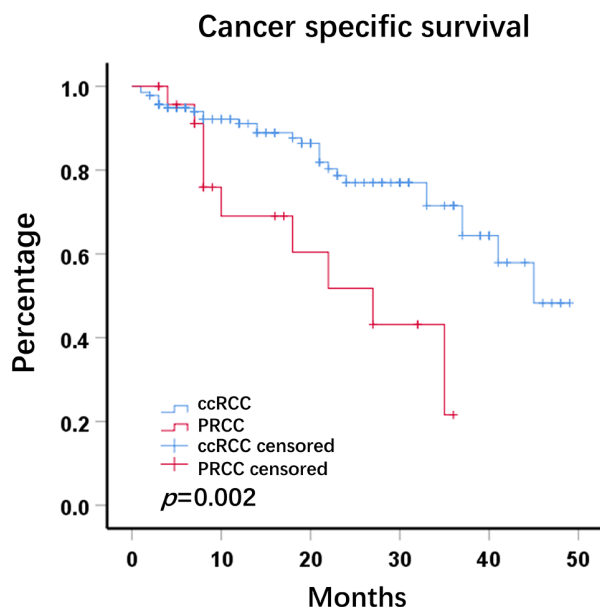
	TYPE-2 PRCC (N=25)	CCRCC (N=138)	P VALUE
Sex, n (%)			.67
Male	20 (75.0%)	105 (76.1%)	
Female	5 (25.0%)	33 (23.9%)	
Age, y, mean \pm SD	60.5 \pm 9.2	56.9 \pm 12.8	.189
BMI, kg/m ² , mean \pm SD	23.8 \pm 3.7	24.2 \pm 2.4	.476
Side, n (%)			.087
Left	13 (52.0%)	47 (34.1%)	
Right	12 (48.0%)	91 (65.9%)	
ASA grade, n (%)			.763
1	1 (4.0%)	6 (4.3.0%)	
2	20 (80.0%)	117 (84.8%)	
3	4 (16%)	15 (10.9%)	
Clinical symptoms, n (%)			.075
No clinical symptoms	1 (4.0%)	37 (26.8%)	
Local symptoms	17 (68.0)	65 (47.1%)	
Systemic symptoms	2 (8.0%)	7 (5.1%)	
Both	5 (20%)	29 (21.0%)	
Clinical N-stage, n (%)			.009
cN0	3 (12.0%)	54 (39.1%)	
cN1	22 (88.0%)	84 (60.9%)	
Clinical M-stage, n (%)			.435
cM0	16 (64.0%)	99 (71.7%)	
cM1	9 (36.0%)	39 (28.3%)	
Mayo classification, n (%)			.450
0	4 (16.0%)	35 (25.4%)	
I	5 (20.0%)	24 (17.4%)	
II	10 (40.0%)	58 (42.0%)	
III	5 (20.0%)	12 (8.7%)	
IV	1 (4.0%)	9 (6.5%)	
Preoperative serum creatinine, μ mol/L, mean \pm SD	100.0 \pm 31.1	92.8 \pm 22.0	.120
Tumor diameter, cm, mean \pm SD	9.1 \pm 3.2	9.0 \pm 2.8	.952
Surgical approach, n (%)			.079
Laparoscope	9 (36.0%)	76 (55.1%)	
Open	16 (64.0%)	62 (44.9%)	
IVC transverse resection, n (%)			.095
No	18 (72.0%)	118 (85.5%)	
Yes	7 (28.0%)	20 (14.5%)	
Operative time, min, mean \pm SD	369.2 \pm 110.7	309.3 \pm 114.5	.877
Surgical blood loss, mL, mean \pm SD	1126.0 \pm 1332.0	1156.3 \pm 1511.1	.224
Sarcomatoid differentiation, n (%)	1 (4.0%)	19 (13.8%)	.171
Serum creatinine 1 week after operation, μ mol/L, mean \pm SD	127.6 \pm 65.7	105.5 \pm 81.6	.334
Postoperative complication, n (%)	10 (40.0%)	38 (27.5%)	.208

Bold means statistically significant.

Table 3. Prognostic factors of 163 cases of renal cell carcinoma (including clear cell renal cell carcinoma and papillary renal cell carcinoma).

ITEMS	UNIVARIABLE ANALYSIS			MULTIVARIABLE ANALYSIS		
	HR	95% CI	P VALUE	HR	95% CI	P VALUE
Sex (M vs F)	1.236	0.578-2.643	0.585			
Age (>58 vs ≤58)	0.861	0.449-1.652	0.653			
Side (L vs R)	0.962	0.494-1.872	0.909			
BMI (>23.8 vs ≤23.8)	0.736	0.377-1.435	0.368			
Size (>9.0 vs ≤9.0)	0.993	0.520-1.895	0.982			
Mayo level						
0	Ref					
1	1.168	0.242-5.639	0.847			
2	0.634	0.105-3.817	0.619			
3	1.824	0.423-7.872	0.420			
4	2.858	0.571-14.318	0.201			
ISUP (high vs low)	1.529	0.735-3.180	0.256			
Lymph (yes vs no)	2.169	1.009-4.662	0.047	1.257	0.568-2.782	0.572
Sarcomatoid (yes vs no)	3.586	1.765-7.285	<0.001	4.893	2.205-10.856	<0.001
Metastasis (yes vs no)	2.872	1.490-5.535	0.002	2.601	1.307-5.176	0.006
Pathology (PRCC vs ccRCC)	3.061	1.448-6.469	0.003	3.337	1.473-7.557	0.004

Bold means statistically significant.

**Figure 3.** The CSS rates of type 2 PRCC-TT and ccRCC-TT.

macrophages along the papillary axis.¹³ Compared with type-1 PRCC, type-2 PRCC is more malignant, and its prognosis is worse.^{14,15} One of the characteristics of RCC is its propensity to invade the venous system, extending into the renal vein or inferior vena cava. Most current studies consider RCC as a whole or

mainly focus on ccRCC with inferior vena cava tumor thrombus. Few studies have reported the influence of histological classification on the prognosis of RCC with tumor thrombus.

By searching keywords such as PRCC and venous tumor thrombus, literature on PRCC with renal vein or inferior vena cava tumor thrombus was identified. We reviewed the literature and summarized the results in Table 4.^{3,16-18} Tilki et al reported 151 cases of PRCC with tumor thrombus between 1971 and 2012 in 2014. As shown in Table 4, the 5-year CSS rates for clear cell carcinoma and PRCC with venous tumor thrombus were 54.8% and 36.8%, respectively. In the multivariate analysis, the pathologic subtype of PRCC was an independent risk factor for the prognosis of patients with tumor thrombus. Papillary renal cell carcinoma remains a risk factor for poor prognosis in patients without lymph node invasion or distant metastasis. However, this study has limitations; the subtypes of PRCC were not differentiated.

There are significant differences in the pathological features and prognosis between type-1 and type-2 PRCC. The tumor cells of type-1 PRCC are small with less cytoplasm, small nuclei, and unclear nucleoli, which are equivalent to Fuhrman nuclear grades 1 and 2. Type-2 PRCC tumors have large cells and abundant cytoplasm, equivalent to Fuhrman nuclear grades 3 and 4. It has been reported that the prognosis of type-1 PRCC is much better than that of type-2 PRCC.^{19,20} Papillary

Table 4. Comparison of clinicopathological characteristics of type-2 papillary renal cell carcinoma with renal vein or inferior vena cava tumor thrombus reported by previous literature and our center.

STUDY	STUDY PERIOD	NUMBER OF PATIENTS	MAYO LEVEL OF THROMBUS (0/I/II/III/IV)	LYMPH NODE METASTASIS	DISTANT METASTASIS	SURGICAL APPROACH	PATHOLOGICAL TYPES	PROGNOSIS
Kim KH ⁷ [2013]	1990-2010	12	0/3/3/4/2	3(25%)	4(33.3%)	Open approach	Type-2 PRCC	The 2- and 5-year CSS were 28.1% and 0%, respectively
Kondo et al ¹⁶ [2013]	1985-2011	7	0/0/4/1/2	1 (14%)	2 (29%)	Open approach	Type-2 PRCC	The median survival was 5.2 months
Tilki et al ¹⁷ [2014]	1971-2012	151	0/27/36/27/20	56(44.8%)	33(31.4%)	Not mentioned	Not distinguished	5-year CSS was 8.5%
Shinagawa et al ¹⁸ [2019]	Not mentioned	1	Mayo III	0	0	Open approach	Type-2 PRCC	12 months after the surgery showed no recurrences or metastases.
Our study [2021]	2016-2020	25	4/5/10/5/1	22 (88.0%)	9 (36.0%)	Laparoscope 9 (36.0%); open 16 (64.0%)	Type-2 PRCC	CSS: 23.5 months

RCC classification was first proposed in 1997. This may be the reason Derya Tilki et al did not differentiate between specific subtypes of PRCC in their cohort. The research period was more than 40 years. Considering that diagnostic tools, surgical techniques, perioperative nursing, surgical indications, and follow-up plans may change over time, the data in this study may not represent the current practice. In particular, the patients in their cohort mainly underwent open surgery.

Other studies on PRCC with venous tumor thrombi are summarized in Table 4. Papillary RCC subtypes have been classified in these studies. A similar conclusion was drawn, that is, type-2 PRCC is a risk factor for prognosis, but the number of cases included was relatively small or simply a case report. In our study, we included the latest data from a larger sample size. We retrospectively analyzed 25 cases of type-2 PRCC and 138 cases of ccRCC and found that the CSS rates of type-2 PRCC and ccRCC with venous thrombus were 23.5 and 38.4 months, respectively. Similar to previous studies, the prognosis of type-2 PRCC with venous tumor thrombus was worse than that of clear cell carcinoma with venous tumor thrombus in our cohort. In addition, our study revealed that sarcomatoid differentiation, distant metastasis, and pathological type were independent risk factors for poor prognosis.

We compared the imaging features of type-2 PRCC with those of clear cell carcinoma. Blood vessels of type-2 PRCC with venous tumor thrombus were not as abundant as those of ccRCC. There was enhancement in the cortical phase, but the degree of enhancement was low. Furthermore, a slight withdrawal of the contrast medium was also observed in the parenchymal and excretory phases. The above imaging findings are helpful for clinicians in making preoperative diagnoses and determining appropriate treatment.^{21,22} According to the results of this study, PRCC is more prone to lymph node metastasis due to its high degree of malignancy. Therefore, more strict renal hilar lymphadenectomy should be carried out to reduce postoperative recurrence and improve prognosis. The patients with PRCC or clear cell carcinoma with tumor thrombus have no obvious difference in the surgical steps and methods of radical nephrectomy and inferior vena cava tumor thrombectomy. In terms of postoperative follow-up, we recommend closer follow-up of PRCC. For patients with residual tumor, lymph node metastasis or distant metastasis, we suggest perioperative systemic treatment.

We compared the imaging features of type 2 PRCC with those of clear cell carcinoma. Blood vessels of type 2 PRCC with venous tumor thrombus were not as abundant as those of ccRCC. There was enhancement in the cortical phase, but the degree of enhancement was low. Furthermore, a slight withdrawal of the contrast medium was also observed in the parenchymal and excretory phases. The above imaging findings are helpful for clinicians in making preoperative diagnoses and determining appropriate treatment.^{21,22}

We compared the differences between the macroscopic and microscopic specimen appearances. Compared with ccRCC, patients with type-2 PRCC with inferior vena cava tumor thrombus had a higher proportion of lymph node invasion. We speculate that this may reflect the malignant potential of type-2 PRCC with venous tumor thrombi. In terms of surgical methods, 36.5% of type-2 PRCCs with thrombi underwent radical nephrectomy and thrombectomy using a laparoscopic approach. In previous studies, most patients underwent open surgery, as shown in Table 4. This is because, in recent years, with the popularization of laparoscopic surgery and the improvement of minimally invasive surgery technology, an increasing number of patients are willing to choose laparoscopic surgery. We have compared laparoscopic surgery with open surgery in terms of surgical difficulty and oncological outcomes in previous literature and found that laparoscopic surgery can achieve similar results to open surgery.

This study had some limitations. Type-2 PRCC consists of at least 3 subtypes, based on molecular and phenotypic features. For example, type-2 PRCC is associated with activation of the NRF2-ARE pathway, and CDKN2A loss and CIMP in type-2 patients have a poor prognosis. There is a lack of information on the molecular and phenotypic features in this study.²³ The small sample of PRCC patients is a major limitation in drawing conclusion. We will carry out multicenter research with large sample size to further clarify the conclusion. For the imaging and pathological features of type-2 PRCC with inferior vena cava tumor thrombus, we did not measure objective data such as CT values in different periods.

In summary, type-2 PRCC has different imaging and pathological characteristics from those of common clear cell carcinoma. Sarcomatoid differentiation, distant metastasis, and pathological subtype were independent risk factors affecting the prognosis. The prognosis of type-2 PRCC with venous tumor thrombus is worse than that of clear cell carcinoma with venous tumor thrombus.

Conclusion

Type-2 PRCC-TT varies with common ccRCC-TT in imaging manifestation and pathological characteristics. The prognosis of type-2 PRCC-TT patients was worse than that of ccRCC-TT patients.

Acknowledgements

The authors thank the entire staff of the Department of Urology, Peking University Third Hospital.

Author Contributions

Conceptualization: L.M. and S.Z.

Data curation: X.Z., M.L., A.A., and Y.L.

Resources: G.Z. and X.Z.

Formal analysis: H.Z., C.L., and Z.D.

Writing-original draft: Z.L. and L.G.

Writing-review and editing: P.H., S.W., and X.T.

Availability of Data and Materials

Research data are not publicly available on legal and ethical grounds. The data sets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Statement of Ethics

Informed written consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Peking University Third Hospital ethics committee. This study was approved by the ethics committee of Peking University Third Hospital, and the ethical batch number was 2018-360-01.

ORCID iD

Lulin Ma  <https://orcid.org/0000-0003-2141-9348>

REFERENCES

- Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European Association of Urology guidelines on renal cell carcinoma: the 2019 update. *Eur Urol.* 2019;75:799-810.
- Mancilla-Jimenez R, Stanley RJ, Blath RA. Papillary renal cell carcinoma: a clinical, radiologic, and pathologic study of 34 cases. *Cancer.* 1976;38:2469-2480.
- Delahunt B, Eble JN. Papillary renal cell carcinoma: a clinicopathologic and immunohistochemical study of 105 tumors. *Mod Pathol.* 1997;10:537-544.
- Beksac AT, Shah QN, Paulucci DJ, et al. Trends and outcomes in contemporary management renal cell carcinoma and vena cava thrombus. *Urol Oncol.* 2019;37:576.e17-576.e23.
- Rodriguez Faba O, Linares E, Tilki D, et al. Impact of microscopic wall invasion of the renal vein or inferior vena cava on cancer-specific survival in patients with renal cell carcinoma and tumor thrombus: a multi-institutional analysis from the international renal cell carcinoma-venous thrombus consortium. *Eur Urol Focus.* 2018;4:435-441.
- Ciancio G, Manoharan M, Katkooi D, De Los Santos R, Soloway MS. Long-term survival in patients undergoing radical nephrectomy and inferior vena cava thrombectomy: single-center experience. *Eur Urol.* 2010;57:667-672.
- Kim KH, You D, Jeong IG, et al. Type II papillary histology predicts poor outcome in patients with renal cell carcinoma and vena cava thrombus. *BJU Int.* 2012;110:E673-E678.
- Liu Z, Zhao X, Ge L, et al. Completely laparoscopic versus open radical nephrectomy and infrahepatic tumor thrombectomy: comparison of surgical complexity and prognosis. *Asian J Surg.* 2021;44:641-648.
- Zhuo L, Guodong Z, Xun Z, et al. A modified surgical technique of shortening renal ischemia time in left renal cancer patients with Mayo level II-IV tumor thrombus. *BMC Surg.* 2020;20:120.
- Liu Z, Tang S, Tian X, et al. Foley catheter-assisted six-step thrombectomy technique in the surgical management of renal cell carcinoma with Mayo level II to IV tumor thrombus. *J Int Med Res.* 2019;47:2104-2115.
- Liu Z, Li L, Hong P, et al. A predictive model for tumor invasion of the inferior vena cava wall using multimodal imaging in patients with renal cell carcinoma and inferior vena cava tumor thrombus. *Biomed Res Int.* 2020;2020:9530618.
- Inamura K. Renal cell tumors: understanding their molecular pathological epidemiology and the 2016 WHO classification. *Int J Mol Sci.* 2017;18:2195.
- Delahunt B, Eble JN, McCreddie MR, Bethwaite PB, Stewart JH, Bilous AM. Morphologic typing of papillary renal cell carcinoma: comparison of growth kinetics and patient survival in 66 cases. *Hum Pathol.* 2001;32:590-595.
- Sukov WR, Lohse CM, Leibovich BC, Thompson RH, Chevillie JC. Clinical and pathological features associated with prognosis in patients with papillary renal cell carcinoma. *J Urol.* 2012;187:54-59.
- Courthod G, Tucci M, Di Maio M, Scagliotti GV. Papillary renal cell carcinoma: a review of the current therapeutic landscape. *Crit Rev Oncol Hematol.* 2015;96:100-112.
- Kondo T, Ikezawa E, Takagi T, et al. Negative impact of papillary histological subtype in renal cell carcinoma extending into the inferior vena cava: single-center experience. *Int J Urol.* 2013;20:1072-1077.
- Tilki D, Nguyen HG, Dall'Era MA, et al. Impact of histologic subtype on cancer-specific survival in patients with renal cell carcinoma and tumor thrombus. *Eur Urol.* 2014;66:577-583.

18. Shinagawa T, Ito H, Sakai Y, et al. Remarkable effect of presurgical nivolumab on originally inoperable papillary renal cell carcinoma with tumor thrombus in inferior vena cava. *Int Cancer ConfJ*. 2019;8:170-174.
19. Pignot G, Elie C, Conquy S, et al. Survival analysis of 130 patients with papillary renal cell carcinoma: prognostic utility of type 1 and type 2 subclassification. *Urology*. 2007;69:230-235.
20. Capitanio U, Cloutier V, Zini L, et al. A critical assessment of the prognostic value of clear cell, papillary and chromophobe histological subtypes in renal cell carcinoma: a population-based study. *BJU Int*. 2009;103:1496-1500.
21. Doshi AM, Ream JM, Kierans AS, et al. Use of MRI in differentiation of papillary renal cell carcinoma subtypes: qualitative and quantitative analysis. *AJR Am J Roentgenol*. 2016;206:566-572.
22. Egbert ND, Caoili EM, Cohan RH, et al. Differentiation of papillary renal cell carcinoma subtypes on CT and MRI. *AJR Am J Roentgenol*. 2013;201:347-355.
23. Cancer Genome Atlas Research Network; Linehan WM, Spellman PT, Rickerts CJ, et al. Comprehensive molecular characterization of papillary renal-cell carcinoma. *N Engl J Med*. 2016;374:135-145.