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Impact of Histologic Subtype on Cancer-specific Survival in Patients with Renal Cell Carcinoma and Tumor Thrombus

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Abstract

Background: Although different prognostic factors for patients with renal cell carcinoma (RCC) and vena cava tumor thrombus (TT) have been studied, the prognostic value of histologic subtype in these patients remains unclear.
Objective: We analyzed the impact of histologic subtype on cancer-specific survival (CSS).
Design, settings, and participants: We retrospectively analyzed the records of 1774 patients with RCC and TT who underwent radical nephrectomy and tumor thrombectomy from 1971 to 2012 at 22 US and European centers.
Outcome measurements and statistical analysis: Multivariable ordered logistic and Cox regression models were used to quantify the impact of tumor histology on CSS.
Results and limitations: Overall 5-yr CSS was 53.4% (confidence interval [CI], 50.5–56.2) in the entire group. TT level (according to the Mayo classification of macroscopic venous invasion in RCC) was I in 38.5% of patients, II in 30.6%, III in 17.3%, and IV in 13.5%. Histologic subtypes were clear cell renal cell carcinoma (cRCC) in 89.9% of patients, papillary renal cell carcinoma (pRCC) in 8.5%, and chromophobe RCC in 1.6%. In univariable analysis, pRCC was associated with a significantly worse CSS ($p < 0.001$) compared with cRCC.

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Prognosis

In multivariable analysis, the presence of pRCC was independently associated with CSS (hazard ratio: 1.62; CI, 1.01–2.61; $p < 0.05$). Higher TT level, positive lymph node status, distant metastasis, and fat invasion were also independently associated with CSS.
Conclusions: In our multi-institutional series, we found that patients with pRCC and vena cava TT who underwent radical nephrectomy and tumor thrombectomy had significantly worse cancer-specific outcomes when compared with patients with other histologic subtypes of RCC. We confirmed that higher TT level and fat invasion were independently associated with reduced CSS.

1. Introduction

Renal cell carcinoma (RCC) represents 2–3% of all cancers [1] with an estimated 65 150 new cases and 13 680 deaths for 2013 in the United States [2]. According to the World Health Organization (WHO), there are at least three major histologic subtypes of RCC: clear cell RCC (cRCC, 80–90%), papillary RCC (pRCC, 10–15%), and chromophobe RCC (chRCC, 4–5%) [3].

Several studies have evaluated the prognostic value of histologic subtype in RCC [4–9]. However, the impact of the three main RCC subtypes on prognosis is inconclusive. Some studies showed a survival advantage for patients with pRCC or chRCC histology relative to that of cRCC, but these reports did not include multivariable analyses [4,6]. Patard et al. performed a multi-institutional international study of 4063 patients and found on multivariable analysis that histopathology was not an independent predictor [9]. This finding was confirmed by Ficarra et al., who analyzed data of patients with centrally reviewed pathology [7]. In contrast, Capitanio et al. reported that histologic subtype as a group was an independent predictor of cancer-specific mortality (CSS) in multivariable analyses using the National Cancer Institute Surveillance Epidemiology and End Results database [5]. Nevertheless, the authors noted that individually neither papillary nor chromophobe histology was distinguishable from clear cell histology. Keegan et al. found that patients with chRCC had improved survival after adjusting for the effect of tumor stage [8]. Pathologic tumor stage remains the strongest prognostic factor in patients with RCC [10]. RCC with tumor thrombus (TT) is found in 4–10% of newly diagnosed RCC patients and associated with poor prognosis, higher Fuhrman grade, and larger tumor size [11]. Although different prognostic factors for patients with RCC and vena cava TT, such as Eastern Cooperative Oncology Group performance status, metastatic status, sarcomatoid features, and concomitant perinephric fat invasion have been extensively documented, the prognostic significance of histologic subtype in patients with RCC and TT has rarely been studied and remains unclear [12,13].

To address this vacuum, we analyzed the impact of histologic subtype on CSS in a large international cohort of RCC patients with TT.

2. Patients and methods

2.1. Patient selection and data collection

This study was approved by the institutional review boards of all participating sites that provided the necessary institutional data-sharing agreements before initiation of the study. A total of 22 US and European centers provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Prior to final analysis, the database was frozen and the final data set was produced for the current analysis. The records of 1774 patients with RCC and vena cava TT who underwent radical nephrectomy and complete tumor thrombectomy between 1971 and 2012 were reviewed. Neoadjuvant and adjuvant treatments were administered at the investigator's discretion to 10.2% of patients, all of whom had metastasis.

2.2. Pathologic evaluation and macroscopic vascular involvement

All surgical specimens were processed according to standard pathologic procedures. Tumor size was evaluated on fixed pathologic specimens. Histologic subtype was determined according to the 1997 WHO Heidelberg classification [14]. pRCC types 1 and 2 were not distinguished in this cohort. Tumor nuclear grade was determined according to the Fuhrman system. Pathologic staging was designated according to the 2009 TNM classification of the American Joint Committee on Cancer [15].

To ensure validity of the pathologic data, two investigators independently reviewed pathology from a subgroup of patients while blinded to patient clinical parameters and the finding of the other reviewer. Interreader reliability measured using the intraclass correlation coefficient was >0.95 for each pathologic characteristic.

2.3. Tumor thrombus level

The Mayo classification was used for the macroscopic vascular involvement [16]. In level I, TT is either at the entry of the renal vein or within the inferior vena cava (IVC) <2 cm from the confluence of the renal vein and the IVC. In level II, TT extends within the IVC >2 cm above the confluence of the renal vein and IVC but still remains below the hepatic veins. In level III, TT involves the intrahepatic IVC. The size of the thrombus ranges from a narrow tail that extends into the IVC to one that fills the lumen and enlarges the IVC. In level IV, TT extends above the diaphragm or into the right atrium.

2.4. Follow-up

Follow-up was performed according to institutional protocols. Patients generally were seen postoperatively at least every 3 mo for the first year, semiannually for the second year, and annually thereafter. Follow-up visits consisted of a physical examination and serum chemistry evaluation including liver function tests and alkaline phosphatase. Diagnostic imaging (eg, ultrasonography, computed tomography of the abdomen/pelvis with intravenous contrast), and chest radiography were performed twice yearly and at the discretion of the treating physician when clinically indicated. When patients died, the cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or

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by death certificates alone. Patients who were identified as having died of RCC had progressive, widely disseminated, and often highly symptomatic metastases at the time of death. Perioperative mortality (death within 30 d of surgery) was censored at time of death for CSS analyses.

2.5. Statistical analysis

The Kaplan-Meier method was used to calculate survival functions (CSS), and differences were assessed with the log-rank statistic. Univariable and multivariable survival analyses were performed using the Cox proportional hazard regression model. In all models, proportional hazards assumptions were systematically verified using the Grambsch-Therneau residual-based test. All reported p values are two sided, and statistical significance was set at $p < 0.05$. No adjustments were made for multiple statistical tests. Data were analyzed using Stata v.11 for Windows (StataCorp, College Station, TX, USA).

3. Results

3.1. Clinical and pathologic characteristics

A total of 1774 patients with RCC and vena cava thrombus underwent radical nephrectomy and tumor thrombectomy from 1971 to 2012 at 22 US and European centers. Mean age in the entire group was 63.3 yr (range: 19–91). Of the 1774 patients, 1594 patients (89.9%) had cRCC, 151 patients (8.5%) had pRCC, and 29 patients (1.6%) had chRCC. TT level (according to the Mayo classification of macroscopic venous invasion in RCC) was level I in 400 patients (38.5%), level II in 318 (30.6%), level III in 180 (17.3%), and level IV in 140 (13.5%). Table 1 compares their clinical and pathologic features. Overall, 21% of patients had positive lymph nodes and 23% of the patients had distant metastases. Higher Fuhrman grade, fat invasion, and pRCC were significantly associated with a higher TT level.

3.2. Clinical outcomes and association of histologic characteristics with survival

Median follow-up was 82.5 mo (interquartile range: 117.2) for patients alive at last follow-up. A total of 1018 patients (57.4%) were deceased at the time of analysis including 712 patients (40.1%) who died of RCC. Overall 5-yr CSS was 53.4% (confidence interval [CI], 50.5–56.2) in the entire patient group.

Five-year CSS estimates in the cRCC, pRCC, and chRCC patients were 54.8% (95% CI, 51.8–57.8), 36.8% (95% CI, 27.0–46.5), and 59.5% (95% CI, 34.5–77.6), respectively (Fig. 1A). In univariable analysis, pRCC was associated with a significantly worse CSS ($p < 0.001$) when compared with cRCC (Table 2; Fig. 1A). This difference in survival remained

Table 1 – Clinical and pathologic characteristics of 1774 patients harboring renal cell carcinoma with tumor thrombus treated at 22 international institutions

	Overall (n = 1774)	cRCC (n = 1594)	pRCC (n = 151)	chRCC (n = 29)
Age, yr (%)				
≤60	613 (38.0)	548 (37.7)	51 (37.8)	14 (56.0)
>60	1000 (62.0)	905 (62.3)	84 (62.2)	11 (44.0)
Mean (range)	63.3 (19–91)	63.4 (19–91)	62.6 (26–89)	60.9 (37–80)
Sex, no. (%)				
Female	621 (35.0)	565 (35.5)	42 (27.8)	14 (48.3)
Male	1153 (65.0)	1029 (64.6)	109 (72.2)	15 (51.7)
TT level (Mayo)				
I	400 (38.5)	366 (40.0)	27 (24.6)	7 (50.0)
II	318 (30.6)	277 (30.3)	36 (32.7)	5 (35.7)
III	180 (17.3)	151 (16.5)	27 (24.5)	2 (14.3)
IV	140 (13.5)	120 (13.1)	20 (18.2)	0 (0.0)
Fuhrman grade, no. (%)				
1	49 (3.7)	43 (3.6)	5 (5.1)	1 (4.6)
2	437 (33.0)	407 (33.8)	22 (22.5)	8 (36.4)
3	633 (47.7)	567 (47.0)	55 (56.1)	11 (50.0)
4	207 (15.6)	189 (15.7)	16 (16.3)	2 (9.1)
T stage, no. (%)				
T3a	666 (37.8)	617 (38.9)	35 (23.8)	14 (48.3)
T3b	769 (43.7)	687 (43.3)	71 (48.3)	11 (37.9)
T3c	228 (13.0)	200 (12.6)	26 (17.7)	2 (6.9)
T4	98 (5.6)	81 (5.1)	15 (10.2)	2 (6.9)
N status, no. (%)				
N0	783 (59.6)	728 (62.2)	43 (34.4)	12 (66.7)
N+	273 (20.8)	214 (18.3)	56 (44.8)	3 (16.7)
Nx	257 (19.6)	228 (19.5)	26 (20.8)	3 (16.7)
Metastasis, no. (%)				
Yes	234 (23.0)	197 (21.9)	33 (31.4)	4 (33.3)
No	782 (77.0)	702 (78.1)	72 (68.6)	8 (66.7)
Fat invasion, no. (%)				
Yes	701 (60.9)	601 (58.9)	90 (79.0)	10 (62.5)
No	450 (39.1)	420 (41.1)	24 (21.1)	6 (37.5)

cRCC = clear cell renal cell carcinoma; chRCC = chromophobe renal cell carcinoma; pRCC = papillary renal cell carcinoma.

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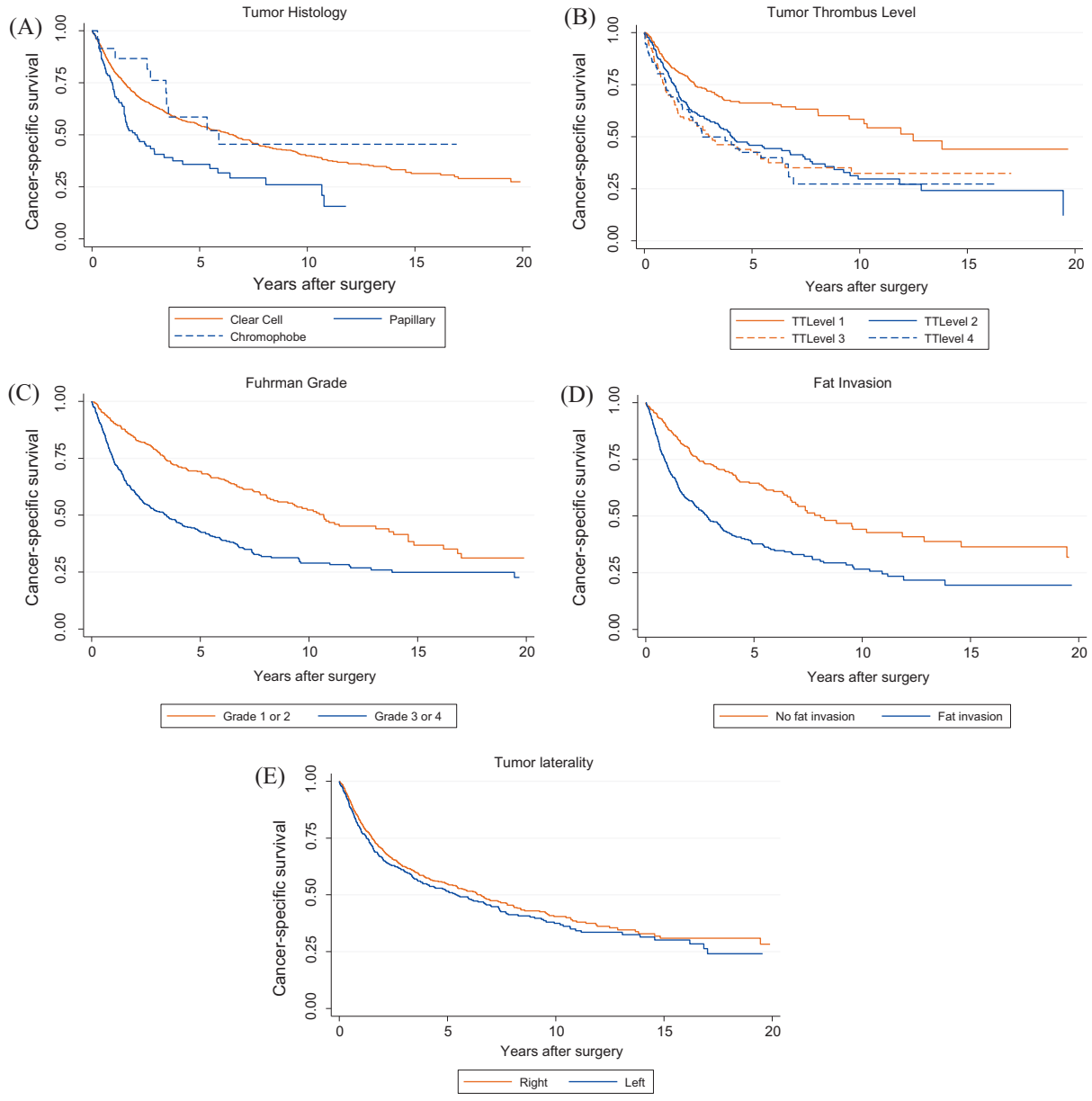

Fig. 1 – Probability estimates of cancer-specific survival in patients with renal cell carcinoma and tumor thrombus stratified by (A) histologic subtype, (B) tumor thrombus level, (C) Fuhrman grade, (D) fat invasion, and (E) tumor laterality. (A–D) The *p* values (log-rank test) were <0.001; (E) the *p* value (log-rank test) was 0.11.

significant when restricting analyses to N0M0 patients (Table 3). Furthermore, TT level, Fuhrman grade, and fat invasion were associated with CSS in univariable analyses (Fig. 1B–D; Table 2). Although the difference was not significant ($p = 0.11$), there was a trend toward inferior survival in patients with left-sided tumors in comparison with right-sided tumors (Fig. 1E).

In multivariable analysis, the presence of pRCC was an independent predictor of CSS (HR: 1.62; CI, 1.01–2.61; $p < 0.05$) (Table 2). Fat invasion and TT level were also independently associated with CSS (Table 2). When analyses were restricted to N0M0 patients, TT level and histology remained significantly associated with CSS in multivariable analysis (Table 3).

4. Discussion

Despite a relatively large body of literature on outcomes after radical surgery in patients with RCC and TT, there are contradictory data on the prognostic significance of TT level and almost no data on the role of the three major histologic subtypes (clear cell, papillary, and chromophobe) in these patients.

The impact of histology has been evaluated for RCC across all tumor stages [4–9]. Some of these studies have reported no prognostic value of histologic subtype [7,9]; others did find a survival benefit for patients with papillary or chromophobe histology compared with clear cell histology [4,6,8]. Only very few studies with small sample

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Table 2 – Univariable and multivariable Cox regression analysis assessing prognostic factors associated with cancer-specific mortality

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
TT level (Mayo)						
I	Ref.					
II	1.79	1.38–2.31	<0.001	2.30	1.61–3.28	<0.001
III	2.04	1.52–2.74	<0.001	1.81	1.18–2.78	<0.01
IV	2.19	1.58–3.02	<0.001	2.16	1.25–3.47	<0.001
Fuhrman grade						
1 or 2	Ref.					
3 or 4	2.07	1.73–2.48	<0.001	1.15	0.79–1.67	0.47
T stage				Due to the collinearity between T stage and TT level, we excluded T stage from the multivariate approach. Inclusion of T stage did not qualitatively alter the results except of TT level.		
T3a	Ref.					
T3b	1.15	0.97–1.37	0.10			
T3c	1.96	1.56–2.47	<0.001			
T4	3.15	2.35–4.21	<0.001			
Nx/N+	Ref.					
N0	0.51	0.42–0.60	<0.001	0.45	0.33–0.62	<0.001
M+	Ref.					
M0	0.35	0.28–0.43	<0.001	0.42	0.30–0.59	<0.001
Fat invasion						
No	Ref.					
Yes	2.07	1.68–2.54	<0.001	1.49	1.10–2.03	<0.01
Histology						
cRCC	Ref.					
chRCC	0.75	0.40–1.41	0.37	1.35	0.31–5.82	0.69
pRCC	1.74	1.37–2.22	<0.001	1.62	1.01–2.61	<0.05

CI = confidence interval; cRCC = clear cell renal cell carcinoma; chRCC = chromophobe renal cell carcinoma; HR = hazard ratio; pRCC = papillary renal cell carcinoma; TT = tumor thrombus.
Multivariable estimations are controlled for age and gender.

Table 3 – Univariable and multivariable Cox regression analysis: N0M0 subgroup

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
TT level (Mayo)						
I	Ref.					
II	2.63	1.67–4.14	<0.001	2.78	1.53–5.05	<0.001
III	2.36	1.38–4.04	<0.01	1.88	0.91–3.89	0.09
IV	3.73	2.21–6.29	<0.001	3.73	2.00–6.97	<0.001
Fuhrman grade						
1 or 2	Ref.					
3 or 4	1.52	0.90–2.55	0.11	1.26	0.74–2.17	0.39
T stage				Due to the collinearity between T stage and TT level, we excluded T stage from the multivariate approach. Inclusion of T stage did not qualitatively alter the results except of TT level.		
T3a	Ref.					
T3b	1.41	0.78–2.54	0.26			
T3c	3.13	1.67–5.88	<0.001			
T4	4.57	1.89–11.04	<0.01			
Fat invasion						
No	Ref.					
Yes	1.12	0.77–1.63	0.57	1.20	0.73–1.98	.48
Histology						
cRCC	Ref.					
chRCC	0.95	0.24–3.86	0.95	3.41	1.52–7.64	<0.01
pRCC	2.08	1.15–3.78	<0.01	2.45	1.21–4.98	<0.05

CI = confidence interval; cRCC = clear cell renal cell carcinoma; chRCC = chromophobe renal cell carcinoma; HR = hazard ratio; pRCC = papillary renal cell carcinoma; TT = tumor thrombus.
Multivariable estimations are controlled for age and gender.

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size exist, which focused on the prognostic role of histologic subtype in RCC patients with TT [17,18].

To address this question, we utilized data of patients with RCC and TT in a large multicenter study. As in reports of RCC of all tumor stages, among the patients with TT in our study, clear cell and papillary variants were the most common. Overall 5-yr CSS was 53.4% in the entire patient group, which is consistent with previous studies showing 5-yr survival rates ranging from 40% to 65% in patients with TT [11–13,17,19].

We found that patients with papillary histopathology had a significantly worse outcome compared with patients with the clear cell or chromophobe subtypes. Papillary histology was significantly associated with CSS in multivariable analysis regardless of other known prognostic clinical and pathologic features such as lymph node metastasis.

Wagner et al. studied prognostic factors for overall survival in patients with RCC extending to the renal vein or the IVC [13]. The authors found that histologic subtype (cRCC vs non-cRCC) was a statistically significant predictor for overall survival in univariable but not in multivariable analysis.

Margulis and colleagues analyzed data of 2157 patients with pRCC ($n = 245$) or cRCC ($n = 1912$) of all stages. Similar to our study, the authors reported that pRCC patients with venous TT had significantly decreased 5-yr CSS compared with patients with cRCC (35% vs 66%) [20]. Overall 5-yr CSS in our study was 37% in pRCC and 55% in patients with cRCC [20].

In a recent study consisting of 74 patients, Kim et al. reported that type II papillary histology predicts poor outcome in patients with RCC and vena cava TT [17]. All 12 patients with pRCC had type II papillary tumors, and 4 of these had metastatic disease.

In a retrospective study composed of 87 patients with RCC and IVC thrombus, Ciancio et al. found that higher nuclear grade, metastasis at presentation, and non–clear cell histology (25 patients) were independent prognostic factors for poor disease-specific survival [18].

Steffens et al. studied the long-term prognosis of pRCC patients compared with patients with cRCC in a large multicenter study including 4941 patients [21]. The authors found a significantly better CSS for patients with nonmetastatic pRCC compared with cRCC. In contrast, in patients with metastatic RCC (N+ and/or M+) at the time of surgery, papillary histology indicated a poor prognosis. The authors hypothesized that one reason for the poor prognosis of metastatic pRCC may be its resistance to immuno- and chemotherapy because novel targeted substances that are also effective in pRCC had not been a treatment option for the vast majority of cases they included [21]. The conflicting results on the impact of papillary histology in the various referenced studies might be observing variations in each study cohort in the ratio of pRCC type 1 and type 2. A high proportion of pRCC type 2 patients might have driven our observations.

In the current study, we found that in addition to histologic subtype, TT level was significantly associated with cancer-specific mortality in multivariable analysis. Some studies have reported decreased survival in patients with TT involving the IVC [19,22–24]; other studies did not find the TT level to be a prognostic indicator [11,12,18,25,26]. Wagner et al. reported a survival benefit for patients with pT3b RCC and only renal vein involvement as compared with pT3b RCC extending into the IVC (according to the 2002 TNM staging classification system) in metastatic and nonmetastatic disease, but they did not find a significant difference according to the level of IVC involvement [13]. In contrast, Martinez-Salamanca and colleagues described TT level as an independent predictor of survival, thus supporting the most recent 2010 TNM staging system [23].

Our study had several important limitations. First and foremost are the limitations inherent to retrospective analyses. Data were not collected prospectively; therefore our multicenter data set is limited because of missing data. Another limitation is the lack of central pathologic review of all specimens and the inability to differentiate types I and II pRCC.

The population in this study underwent surgery by multiple surgeons with different techniques and approaches to thrombectomy. However, this can be construed as a strength because it stands for real-world practice, making the conclusions of the study more generalizable. The analysis of patients treated in referral centers may have biased the results. Finally, the study period spans >40 yr, and the data in the present study may not represent current practice patterns, considering that diagnostic tools, surgical techniques, perioperative care, indication for surgery, and follow-up protocols might have changed over time. However, 27.1% of the patients in the study were treated in the 1990s, and 62.8% in the year 2000 or after, which may limit the relevance of such issues. Despite these limitations, to our knowledge, this study is the largest including multivariable analyses to date on the role of histologic subtype in patients with RCC and TT.

5. Conclusions

In this large multi-institutional international cohort, we found that patients with pRCC and vena cava TT who underwent radical nephrectomy and tumor thrombectomy had significantly worse cancer-specific outcomes and a higher TT level when compared with patients with other histologic subtypes of RCC. This strong association of papillary histology with adverse outcome was independent of nodal status and the presence of distant metastasis or other clinicopathologic features. Consideration of histologic subtype may help in the decision making for risk-adapted follow-up. Randomized trials are underway to test adjuvant targeted therapies with the possibility that future drugs/trials may target specific histology.

Author contributions: Derya Tilki had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tilki, Evans.
Acquisition of data: Tilki, Nguyen, Dall'Era, Bertini, Carballido, Chromecki, Ciancio, Daneshmand, Gontero, Gonzalez, Haferkamp, Hohenfellner, Huang, Koppie, Lorentz, Mandel, Martinez-Salamanca, Master, Matloob,

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References

[1] Ljungberg B, Cowan NC, Hanbury DC, et al. EAU guidelines on renal cell carcinoma: the 2010 update. Eur Urol 2010;58:398–406.
[2] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
[3] Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Pathology and genetics of tumours of the urinary system and male genital organs. World Health Organization classification of tumours. Lyon, France: IARC Press; 2004. p. 7.
[4] Amin MB, Tamboli P, Javidan J, et al. Prognostic impact of histologic subtyping of adult renal epithelial neoplasms: an experience of 405 cases. Am J Surg Pathol 2002;26:281–91.
[5] 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;103:1496–500.
[6] Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol 2003;27:612–24.
[7] Ficarra V, Martignoni G, Galfano A, et al. Prognostic role of the histologic subtypes of renal cell carcinoma after slide revision. Eur Urol 2006;50:786–94, discussion 793–4.
[8] Keegan KA, Schupp CW, Chamie K, Hellenthal NJ, Evans CP, Koppie TM. Histopathology of surgically treated renal cell carcinoma: survival differences by subtype and stage. J Urol 2012;188:391–7.
[9] Patard JJ, Leray E, Rioux-Leclercq N, et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J Clin Oncol 2005;23:2763–71.
[10] Ficarra V, Novara G, Iafrate M, et al. Proposal for reclassification of the TNM staging system in patients with locally advanced (pT3–4) renal cell carcinoma according to the cancer-related outcome. Eur Urol 2007;51:722–31, discussion 729–31.
[11] Hatcher PA, Anderson EE, Paulson DF, Carson CC, Robertson JE. Surgical management and prognosis of renal cell carcinoma invading the vena cava. J Urol 1991;145:20–3, discussion 23–4.
[12] Klatte T, Pantuck AJ, Riggs SB, et al. Prognostic factors for renal cell carcinoma with tumor thrombus extension. J Urol 2007;178:1189–95, discussion 1195.
[13] Wagner B, Patard J-J, Méjean A, et al. Prognostic value of renal vein and inferior vena cava involvement in renal cell carcinoma. Eur Urol 2009;55:452–60.
[14] Storkel S, Eble JN, Adlakha K, et al. Classification of renal cell carcinoma: Workgroup No. 1. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer 1997;80:987–9.
[15] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
[16] Neves RJ, Zincke H. Surgical treatment of renal cancer with vena cava extension. Br J Urol 1987;59:390–5.
[17] 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:E673–8.
[18] Ciancio G, Manoharan M, Katkoori 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;57:667–72.
[19] Haferkamp A, Bastian PJ, Jakobi H, et al. Renal cell carcinoma with tumor thrombus extension into the vena cava: prospective long-term followup. J Urol 2007;177:1703–8.
[20] Margulis V, Tamboli P, Matin SF, Swanson DA, Wood CG. Analysis of clinicopathologic predictors of oncologic outcome provides insight into the natural history of surgically managed papillary renal cell carcinoma. Cancer 2008;112:1480–8.
[21] Steffens S, Janssen M, Roos FC, et al. Incidence and long-term prognosis of papillary compared to clear cell renal cell carcinoma—a multicentre study. Eur J Cancer 2012;48:2347–52.
[22] Leibovich BC, Cheville JC, Lohse CM, et al. Cancer specific survival for patients with pT3 renal cell carcinoma—can the 2002 primary tumor classification be improved? J Urol 2005;173:716–9.
[23] Martinez-Salamanca JI, Huang WC, Millan I, et al. Prognostic impact of the 2009 UICC/AJCC TNM staging system for renal cell carcinoma with venous extension. Eur Urol 2011;59:120–7.
[24] Quek ML, Stein JP, Skinner DG. Surgical approaches to venous tumor thrombus. Semin Urol Oncol 2001;19:88–97.
[25] Kim HL, Zisman A, Han KR, Figlin RA, Belldegrun AS. Prognostic significance of venous thrombus in renal cell carcinoma. Are renal vein and inferior vena cava involvement different? J Urol 2004;171:588–91.
[26] Ljungberg B, Stenling R, Osterdahl B, Farrelly E, Aberg T, Roos G. Vein invasion in renal cell carcinoma: impact on metastatic behavior and survival. J Urol 1995;154:1681–4.

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