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Kidney Cancer

Prognostic Impact of the 2009 UICC/AJCC TNM Staging System for Renal Cell Carcinoma with Venous Extension

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Abstract

Background: The prognostic significance of venous involvement and tumour thrombus level in renal cell carcinoma (RCC) remains highly controversial. In 2010, the American Joint Committee on Cancer (AJCC) and the Union International Centre le Cancer (UICC) revised the RCC staging system (7th edition) based on tumour thrombus level, differentiating the T stage of tumours limited to renal-vein-only involvement.
Objective: We aimed to evaluate the impact of tumour thrombus extension in a multi-institutional cohort of patients.
Design, setting, and participants: An international consortium of 11 institutions was established to retrospectively review a combined cohort of 1215 patients undergoing radical nephrectomy and tumour thrombectomy for RCC, including 585 patients with inferior vena cava (IVC) involvement or higher.

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Measurements: Predictive factors of survival, including histology, tumour thrombus level, nodal status, Fuhrman grade, and tumour size, were analysed.
Results and limitations: A total of 1122 patients with complete data were reviewed. The median follow-up for all patients was 24.7 mo, with a median survival of 33.8 mo. The 5-yr survival was 43.2% (renal vein involvement), 37% (IVC below the diaphragm), and 22% with caval involvement above the diaphragm. On multivariate analysis, tumour size (hazard ratio [HR]: 1.64 [range: 1.03–2.59]; $p = 0.036$), Fuhrman grade (HR: 2.26 [range: 1.65–3.1]; $p = 0.000$), nodal metastasis (HR: 1.32 [range: 1.09–1.67]; $p = 0.005$), and tumour thrombus level (HR: 2.10 [range: 1.53–3.0]; $p = 0.00$) correlated independently with survival.
Conclusions: Based on analysis of the largest known cohort of patients with RCC along with IVC and atrial thrombus involvement, tumour thrombus level is an independent predictor of survival. Our findings support the changes to the latest AJCC/UICC staging system.

1. Introduction

The incidence of kidney cancer continues to rise, with approximately 57 760 newly diagnosed cases of renal cell carcinoma (RCC) in the United States in 2009 [1]. Although the greatest proportion of newly diagnosed patients with RCC present with stage I (localised) disease, nearly 1/3 of patients present with stage III/IV RCC [2]. According to the US National Cancer Database (2001–2002), patients with stage I RCC have an 81% 5-yr survival, while stage III and stage IV patients have a 53% and 8% 5-yr survival, respectively [3]. Thus, advanced-stage RCC remains highly lethal, accounting for roughly 13 000 deaths, or 4% of all cancer-related deaths in the United States in 2009 [2].

RCC presents with venous extension or tumour thrombus in 4–10% of newly diagnosed patients [4]. The level of venous involvement, however, varies widely. Using the Libertino classification system [5]. Renal-vein-only involvement occurs in 30–78% of patients with tumour thrombus. Level 1 caval involvement (inferior vena cava [IVC] below the diaphragm) occurs in 16–48% of patients, while level 2 (IVC above the diaphragm) involvement occurs in 4–25% of cases [5–9]. Level 3 involvement (into the atrium) is rare, occurring in only 2–11% [5,10,11].

The significance of venous involvement and the cephalad extent of tumour thrombus remains highly controversial. It is well documented that RCCs with tumour thrombus are aggressive tumours, associated with poor prognosis, higher Fuhrman grades, larger size or sarcomatoid features, and N+ or M+ disease at the time of surgery [6]. Not surprisingly, patients with tumour thrombus have higher recurrence rates and lower rates of cancer-specific survival (CSS) [6,12,13]. However, multiple studies have demonstrated that when adjusting for clinical and pathologic features (Fuhrman grade, stage, Eastern Cooperative Oncology Group [ECOG] performance status), the thrombus itself does not affect CSS [6,14].

When examining the prognostic significance of the cephalad extent of tumour thrombus, the data become increasingly conflicting. Some studies have demonstrated survival differences based on the level of TT [15–17], but other series have demonstrated no worsening of survival based on the level of tumour thrombus [18,19]. The greatest source of contention appears to revolve around the significance of renal vein versus level 1 involvement. Although some investigators have demonstrated no CSS differences between the two [6,7,13,17], a few contemporary series have suggested a long-term survival advantage in patients with involvement limited to the renal vein versus IVC below the diaphragm (level 1) [5,9]. In addition, it has been suggested that N+ or M+ disease at the time of surgery is unrelated to tumour thrombus level [5]. These findings, along with increasing knowledge of the significance of fat (sinus and perinephric) and adrenal invasion, have prompted several institutions and cooperative groups to advocate adjustments to the TNM classification to improve its prognostic accuracy [8,18,20,21]. Recently, an updated staging system by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) was published [22]. Although the previous system (2002; 6th edition) categorised RCCs with renal vein and level 1 involvement as pT3b tumours, the new system (7th edition) designates renal vein involvement as pT3a and level 1 involvement as pT3b [22].

The International Renal Cell Carcinoma–Venous Thrombus Consortium (IRCCVTC) was created with the aim of characterising prognostic factors that closely determine the natural history of patients with RCC presenting with tumour thrombus. In this study, the consortium set out to evaluate the newly revised TNM system by investigating the impact of renal vein versus IVC involvement below the diaphragm (pT3a vs pT3b) as well as the impact of infradiaphragmatic versus supradiaphragmatic IVC involvement (pT3b vs pT3c).

2. Material and methods

2.1. Patient selection

The institutional review board from each of the 11 participating sites approved this multicentre study from the IRCCVTC. A centralised database was generated for data storage, analysis, and validation. Data integrity was achieved, and the database was frozen against additional

Table 1 – Patient characteristics. Numbers in parentheses are percentages

	Renal vein $n = 537$	Level 1 (below) $n = 355$	Level 2 (above) $n = 153$	Level 3 (atrium) $n = 77$
Age, yr (%)				
<60	226 (42.1)	147 (41.4)	73 (47.7)	38 (49.4)
>60	311 (57.9)	208 (58.6)	80 (52.3)	39 (50.6)
Mean (range)	62 (25–91)	62 (19–88)	61 (27–82)	62 (25–84)
Sex, No. (%)				
Female	177 (33.0)	111 (31.3)	55 (35.9)	33 (42.9)
Male	360 (67.0)	244 (68.7)	98 (64.1)	44 (57.1)
Histologic category, No. (%)				
Clear cell	437 (91.2)	290 (89.0)	124 (89.9)	55 (90.2)
Papillary	12 (2.5)	13 (4.0)	7 (5.1)	3 (4.9)
Chromophobe	11 (2.3)	7 (2.1)	1 (0.7)	1 (1.6)
Other	19 (4.0)	16 (4.9)	6 (4.3)	2 (3.3)
Tumour size, No. (%)				
<4 cm	36 (7.1)	19 (5.4)	8 (5.4)	2 (2.7)
4–7 cm	131 (25.8)	83 (23.5)	29 (19.3)	21 (27.6)
>7 cm	341 (67.1)	251 (71.1)	113 (75.3)	53 (69.7)
Mean (range)	9.1 (1–30)	9.7 (2–29)	9.9 (3–25)	9.9 (2–20)
Fuhrman grade, No. (%)				
I	33 (6.6)	10 (3.2)	3 (2.2)	1 (1.8)
II	202 (40.6)	115 (37.3)	50 (37.0)	16 (29.1)
III	218 (43.9)	143 (46.4)	63 (46.7)	34 (61.8)
IV	44 (8.9)	40 (13.0)	19 (14.1)	4 (7.3)
N status, No. (%)				
N0	384 (71.5)	199 (56.1)	72 (47.1)	45 (58.4)
N+	96 (17.9)	96 (27.0)	41 (26.8)	13 (16.9)
Nx	57 (10.6)	60 (16.9)	40 (26.1)	19 (24.7)
Fat invasion, No. (%)				
No	164 (55.2)	120 (49.4)	31 (45.6)	45 (77.6)
Yes	133 (44.8)	123 (50.6)	37 (54.4)	13 (22.4)
Metastasis, No. (%)				
No	399 (74.3)	268 (75.5)	119 (77.8)	64 (83.1)
Yes	138 (25.7)	87 (24.5)	34 (22.2)	13 (16.9)

modification. A definitive data set was generated for the present analysis. The records of 1215 patients who underwent radical nephrectomy and complete tumour thrombectomy from 1970 to 2006 at 11 US and European academic institutions (Lahey Clinic; Memorial Sloan-Kettering Cancer Centre; University of Miami; Wayne State University; University of California, Davis; University of Heidelberg; Vita-Salute San Raffaele; University of Eastern Piedmont; Fundació Puigvert; Hospital Universitario Gregorio Marañón; Hospital Universitario Puerta de Hierro-Majadahonda) were reviewed. Ninety-three patients (7.3%) were excluded because of lack of confirmation of thrombus level and pathologic information or incomplete resection/bulky venous disease, resulting in a total of 1122 patients available for analysis. Clinicopathologic and follow-up information was documented in the respective institutional cancer registries.

2.2. Study variables

We analysed the following variables: age, gender, tumour size, thrombus level, time to death or last follow-up, cause of death, histologic category, fat invasion, adrenal invasion, Fuhrman grade, metastasis at the time of surgery, and pT and pN stage.

2.3. Assessment of pathologic variables

Each institution reviewed the pathologic slides according to standard protocol. Tumour size was evaluated on fixed pathologic specimens. Histologic subtype was determined according to the 1997 World Health Organisation Heidelberg classification [23]. Tumour nuclear grade was determined according to the Fuhrman system. Pathologic staging was designated according to the 2009 TNM classification of AJCC [22]. Stage pT3a was defined as a tumour thrombus extension into the renal vein and pT3b as any venous extension into the IVC below the diaphragm. Stage pT3c was defined as a tumour thrombus extension into the IVC above the diaphragm.

2.4. Statistical analysis

The treating physicians defined the cause of death by chart review or by death certificates alone. Perioperative mortality (any death within 30 d of surgery or before discharge) was censored at the time of death for the CSS analyses. For the initial analysis, the student t test was used to compare the means of the continuous variables among groups, and the results were expressed as mean plus or minus standard deviation (SD). The comparison between categorical variables was evaluated by the χ^2 test. Overall survival distribution was estimated by Kaplan-Meier method, and differences between groups were tested using the log-rank test. A Cox proportional hazard univariate and multivariate analysis was also performed, including relative risk and confidence intervals (CI). Finally, the Cox proportional risk regression model was fitted to data to estimate the independent prognostic importance of survival. The model's basic assumptions were evaluated (proportional hazards). All p values were two-sided, and values ≤ 0.05 were considered to indicate statistical significance. Analyses were performed using SPSS v.14 (SPSS, Chicago, IL, USA).

3. Results

3.1. General characteristics

A total of 1122 patients underwent radical nephrectomy and tumour thrombectomy for RCC at 11 institutions. There

Table 2 – Cancer-specific survival (5 yr) according to tumour thrombus level, N/M status, and long-term survival (5 and 10 yr) according to tumour thrombus level pTNM

	Global	Renal vein		Level 1		Level 2		Level 3	
	5-yr CSS, no. (SE)	No.	5-yr CSS, no. (SE)	No.	5-yr CSS, no. (SE)	No.	5-yr CSS, no. (SE)	No.	5-yr CSS, no. (SE)
N0M0	50 (2.3)	304	55 (3.2)	165	55 (4.3)	59	36 (7.1)	40	17 (6.2)
M1	16 (2.5)	138	16 (3.5)	87	15 (4.2)	34	15 (7.2)	13	17 (11)
N+	26 (4.3)	96	27 (5.0)	96	25 (4.9)	41	18 (6.9)	13	17 (11)
N+M1	25 (7.2)	50	35 (7.5)	57	24 (6.4)	26	23 (9.8)	7	28 (17)

	5-yr CSS, no. (SE)	10-yr CSS, no. (SE) 10-yrs CSS*
Renal vein (pT3a)	43.2 (2.4)	23 (2.3)
Level 1 (pT3b)	37.3 (2.8)	21.2 (2.8)
Renal vein plus level 1 (2002 pT3b)	40.9 (1.8)	22.3 (1.8)
Level 2 + 3 (pT3c)	22.2 (3.2)	13.2 (2.8)

CSS = cancer-specific survival; SE = standard error.

were 376 females (33.5%) and 746 males (66.5%). Mean age was 61.8 yr of age (range: 19–90), and median tumour size 9.5 cm (range: 1–30). Patient characteristics are summarised in Table 1. At the time of analysis, 618 patients (60%) were dead of disease, 118 patients (11.2%) died of other causes, 143 patients (13.6%) were alive with disease, and 169 patients (16.2%) were alive with no evidence of disease. The global perioperative mortality rate (first 30 d after surgery) was 4.2% (44 patients). The greatest perioperative mortality rate was seen in the level 3 group, with renal vein at 3–6%, level 1 at 5.4%, level 2 at 4.3%, and level 3 at 19.4% ($p < 0.001$).

3.2. *Survival analysis and predictive factors*

We excluded 74 patients from survival analysis because of lack of follow-up data. Median follow-up in all patients (1048) was 24.7 mo (range: 0.1–290). Overall median survival time was 33.8 mo (range: 29.4–38.2), and median follow-up for surviving patients was 52.5 mo (range: 0.1–290). The 5-yr CSS for each level according to N and M status is shown in Table 2.

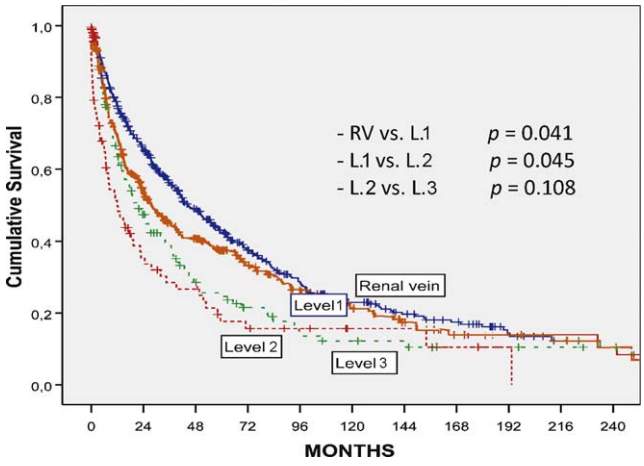

Fig. 1 – Kaplan-Meier cancer-specific survival in patients with renal cell carcinoma and tumour thrombus classified by tumour thrombus level. RV = renal vein.

Overall median survival time by tumour thrombus level was 44.6 mo (renal vein), 27.9 mo (level 1), 21.4 mo (level 2), and 12 mo (level 3; Fig. 1). There was a difference in 5- and 10-yr CSS between patients with thrombus in the renal vein only, the IVC, or above the diaphragm (Fig. 1; Table 2). If we consider specifically 5-yr CSS in patients with renal vein (2009 pT3a) versus level 1 (2009 pT3b) disease, there was a statistically significant difference ($p < 0.005$)—43.2 ± 2.4 SD versus 37.3 ± 2.8 SD—in patients with any N and any M disease (Fig. 2A) but not in patients with N0M0 disease (Fig. 2B). Median 5-yr CSS for T3b (level 1) disease was 37.3 ± 2.8 SD and for T3c (level 2 + 3) disease was 22.2 ± 3.2 SD ($p = 0.002$; Fig. 2C).

Univariate Cox regression analysis demonstrated that Fuhrman grade (II and III; $p < 0.001$), tumour size (>7 cm; hazard ratio [HR]: 1.6; $p < 0.001$), fat invasion ($p < 0.001$), N+ ($p < 0.001$; HR: 1.7), M+ ($p < 0.001$; HR: 2.3), and tumour thrombus level (2 and 3; $p < 0.001$) were statistically significant predictors for CSS (Table 3). Age, gender, tumour histology, and adrenal invasion did not affect CSS.

In multivariate analysis (Table 3), tumour size, Fuhrman grade, fat invasion, N+, M+, and tumour thrombus level (2 and 3) remained independent predictive factors of CSS. Excluding patients with renal vein invasion, the same covariates remained statistically significant (Table 3).

4. Discussion

4.1. *Renal vein (pT3a 2009) versus inferior vena cava below the diaphragm (pT3b 2009) survival differences*

In 2004, two controversial papers examined the accuracy of the 2002 TMN staging system in predicting prognosis in patients with RCC and tumour thrombus below the diaphragm [6,5]. Kim et al [6], Staehler et al [24], Ljungberg et al [17], and Klatte et al [25] demonstrated that the extent of venous involvement (renal vein vs IVC) did not have any impact on the survival rate, supporting the 2002 staging system (pT3b). Conversely, Moinzadeh et al [5], Blute et al [15], Leibovich et al [20], Gettman et al [16], Klaver et al [19], and recently Wagner et al [9] demonstrated in their respective series that patients with tumour thrombus

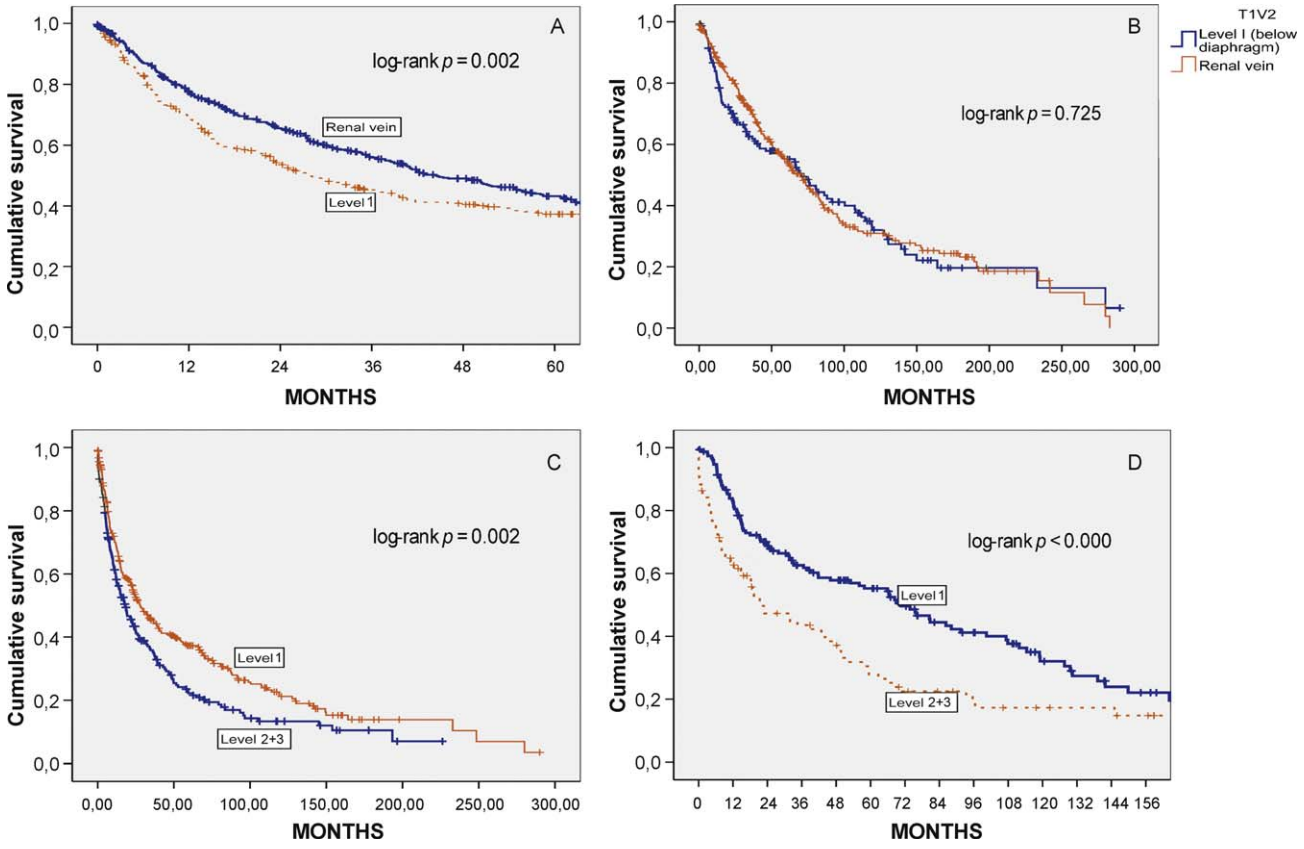

Fig. 2 – (A) Kaplan-Meier cancer-specific survival (CSS) in patients with renal vein (pT3a) versus level 1 (pT3b) with any N and any M; (B) Kaplan-Meier CSS in patients with renal vein (pT3a) versus level 1 (pT3b) N0M0 patients; (C) Kaplan-Meier CSS in patients with level 1 (pT3b) versus level 2 + 3 (pT3c) with any N and any M; (D) Kaplan-Meier CSS in patients with level 1 (pT3b) versus level 2 + 3 (pT3c) N0M0 patients.

Table 3 – Univariate and multivariate Cox regression analysis

Covariates	Univariate analysis			Multivariate analysis			Multivariate analysis (excluding renal vein)		
	p value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI
Tumour size									
<4 cm									
4–7 cm	0.24	1.24	0.86–1.78	0.036	1.64	1.03–2.59	0.007	3.23	1.38–7.58
>7 cm	0.003	1.66	1.18–2.33	0.003	1.94	1.25–2.98	0.003	3.69	1.63–8.36
Fuhrman grade									
I + II									
II	<0.001	1.74	1.47–2.06	0.000	1.55	1.28–1.87	0.003	1.51	1.15–1.97
III	<0.001	2.62	2.0–3.43	0.000	2.26	1.65–3.1	0.014	2.26	1.11–2.66
N (node status)									
N0									
N+	<0.001	1.76	1.48–2.1	0.005	1.32	1.09–1.67	0.014	1.39	1.07–1.81
M (metastasis)									
M0									
M1	<0.001	2.35	1.99–2.76	0.000	2.10	1.72–2.54	0.000	1.69	1.27–2.24
Fat invasion									
Yes									
No	<0.001	1.96	1.61–2.38	0.000	1.10	1.50–2.60	0.000	1.86	1.50–2.30
Tumour thrombus level									
Renal vein									
Level 1	0.39	1.19	1.01–1.41	0.42	1.08	0.89–1.31			
Level 2	<0.001	1.53	1.23–1.91	0.13	1.25	0.94–1.65			
Level 3	<0.001	2.00	1.51–2.64	0.00	2.10	1.53–3.0	0.027	1.33	1.03–1.71

HR = hazard ratio; CI = confidence interval.

Table 4 – Comparative series (renal vein vs inferior vena cava and 2002 pT3b vs pT3c)

Author	Period	No. of centres	Renal vein		*p* value	pT3b		*p* value
			IVC BD			pT3c		
Kim et al [6]	1989–2001	1	41	28	0.575	28	12	0.02*
Moinzadeh et al [5]	1970–2000	1	46	68	0.0001*	68	39	0.48
Haferkamp et al [10]	1993–2005	1	23	76	–	99	12	0.032*
Leibovich et al [20]	1970–2000	1	283	139	<0.001*	139	19	–
Staehler et al [24]	1987–1998	1	19	51	NS	51	10	0.6
Ljungberg et al [17]	1982–1993	1	47	19	0.95	19	7	NS
Klatte et al [25]	1985–2006	1	166	137	0.28	137	18	0.52
Glazer et al [27]	1984–1993	1	–	–	–	10	8	NS
Gettman et al [16]	1970–1998	1	127	160	0.048*	–	–	–
Blute et al [15]	1970–2000	1	191	171	0.002*	–	–	–
Klaver et al [19]	1990–2006	1	50	51	0.003*	–	–	–
Bissada et al [26]	1973–1999	1	–	–	–	39	15	NS
Wagner et al [9]	–	13	933	196	<0.001*	196	63	0.613
Martinez-Salamanca et al	1962–2006	11	537	355	<0.005*	355	230	<0.005*

IVC = inferior vena cava; BD = below the diaphragm; NS = no statistically significant differences.
* Statistically significant.

involving the renal vein only were less likely to die of RCC compared to those with IVC involvement, supporting the 2009 revision in pT staging (new TNM change; Table 4).

All of the aforementioned studies (except for Wagner et al [9]) are limited by single institution experiences. To increase the number of patients in each tumour thrombus category, we created an international consortium of centres to examine the impact of tumour thrombus level on outcomes and to analyse the new 2009 TMN revisions changes. Our results demonstrate that patients with only renal vein involvement enjoy improved 5-yr CSS compared to those with IVC extension below the diaphragm ($p < 0.002$). At 10-yr follow-up, the survival differences are less marked but still persist ($p = 0.037$; Fig. 2; Table 2). Based on these findings, we believe that the 2009 TNM changes are valid.

Nonetheless, regardless of tumour thrombus level, the 5- and 10-yr CSS for these patients remains poor, with many of the deaths occurring with 5 yr of surgery (Table 3). Many authors have previously pointed out the importance of preexisting M+ or N+ at the time of surgery. In our current series, tumour thrombus level (renal vein vs level 1) did not affect CSS in N0M0 patients ($p = 0.725$; Fig. 2B; Table 2).

4.2. *pT3b versus pT3c survival differences*

The 2009 TNM staging system differentiates pT stage based on the level of tumour thrombus. Some series do support this separation because they failed to demonstrate prognostic significance based on tumour thrombus level [5,9,17,24–27]. The lack of significance, however, may be the result of small numbers of patients with pT3c disease in previously published series, which were primarily based on single-institution/surgeon experiences (Table 4). In the only published multi-institutional study by Wagner et al [9], the authors were still limited by a relatively low number of patients with supradiaphragmatic disease (pT3c; $n = 63$). In comparison, in our series of 230 pT3 patients, there was a statistically significant survival difference compared to those with pT3b disease ($p = 0\ 002$), again supporting the new TNM (Fig. 2C and D; Table 2). The survival differences persist regardless of N and M status (Fig. 2D) as well as on multivariate analysis (Table 3).

4.3. *N+ and/or M1 patients*

Advanced disease at the time of diagnosis (N+ and/or M1) has been shown to be an independent predictor of decreased survival regardless of venous involvement [5,6,10,15,16,27,28]. It has been suggested, however, that nodal involvement may be related to tumour thrombus level [16,26,27]: This remains controversial, as some investigators have failed to find an association between tumour thrombus level and N status [5,29].

In our series, there is a relationship between tumour thrombus level and N status. It appears that a more cephalad tumour thrombus level is associated with positive nodal status (renal vein: 20%; level 1: 32%; and level 2: 36%; Table 2). This data suggest that a higher tumour thrombus level may be associated with advanced disease. Conversely, in this series, there was no clear association between M+ disease and tumour thrombus level (Table 2).

As with other series [9,10,15], we found that tumour size and Fuhrman grade are independent predictors of CSS in both univariate and multivariate analysis. Tumour size > 7 cm and Fuhrman grade III or IV were the strongest predictors of worse survival ($p < 0.000$; Table 3).

Because N+ and M+ disease are known factors of a poor prognosis, we analysed a different subgroup of patients according to their N–M status. We found a reduced 5-yr CSS between N0M0 patients and N+M1 regardless of tumour thrombus level (renal vein: 55% vs 35%; level 1: 55% vs 24%; level 2: 36% vs 23%; Table 2). Interestingly, some N+M1 patients faired better than those M1 or N1 patients alone. These findings, however, were not statistically significant.

4.4. *Perioperative mortality and adrenal/fat involvement*

Several factors had been related with perioperative mortality, including patient comorbidities, M+ status, and tumour thrombus extension above the diaphragm [15,24,26,30].

Even in this "very high risk" surgery cohort, global perioperative mortality remained acceptable (6%) and comparable to other series (3–10%) [4,10,11,15,24,30]. Not surprisingly, the highest perioperative mortality rates were observed in patients with atrial involvement (19.4%), which is lower than in other series [24]. In our cohort, several centres and surgeons were involved employing various techniques and approaches to thrombectomy. However, it is beyond the scope of this study to suggest a relationship between surgical technique and perioperative mortality.

Similar to other authors [19,20], we found that perinephric/renal sinus fat invasion is an independent predictor factor of death ($p < 0\,001$; HR: 1.96). Our retrospective multicentre data set is limited because of significant missing data regarding fat invasion (specifically, renal sinus fat), ECOG status, and adrenal involvement. Therefore, we were unable to perform a subgroup analysis of these prognostics variables and limited our conclusions to tumour thrombus level survival analysis.

Our study has limitations worth mentioning. Because IVC and atrial involvement are relatively uncommon, a consortium of high-volume institutions was necessary to accrue a significant and meaningful cohort of patients. Therefore, the data were not prospectively collected in a uniform fashion. Not surprisingly, we did not have reliable data for several variables that likely affect survival, including perinephric/sinus fat involvement and surgical technique. Nonetheless, to our knowledge, this consortium represents the largest group of patients with RCC and caval involvement, nearly doubling the number of patients with IVC involvement from a previous series and quadrupling the number of patients with atrial involvement.

5. Conclusions

There remains controversy regarding the prognostic significance of tumour thrombus involvement, resulting in a new staging system released by the AJCC and UICC in 2009. Our study represents one of the largest tumour thrombus series and contains the largest cohort of patients with supradiaphragmatic disease. The results from our study demonstrate significant survival differences in patients with renal-vein-only involvement as well as difference based on the cephalad extent of tumour thrombus, supporting the newly revised staging system. In addition, tumour size, Fuhrman grade, fat invasion, N+, and M+ remain stronger independent predictors for survival in patients with RCC and venous involvement.

Author contributions: Juan I. Martínez-Salamanca 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.

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Acquisition of data: Martínez-Salamanca, Ciancio, Russo, Libertino, Carballido, Hernández, Montorsi, Terrone, Palou, Haferkamp, Pontes, Hu.
Analysis and interpretation of data: Martínez-Salamanca, Huang, Bianco, Libertino.
Drafting of the manuscript: Martínez-Salamanca, Huang, Bianco, Koppie.
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