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Original Article

Venous tumor thrombus consistency is not predictive of survival in patients with renal cell carcinoma: A retrospective study of 147 patients

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Abbreviations & Acronyms
CSS = cancer-specific survival
fVTTC = friable venous tumor thrombus consistency
HR = hazard ratio
IDI = integrated discrimination improvement index
NRI = net reclassification index
OS = overall survival
RCC = renal cell carcinoma
ROC = receiving operator characteristic
RSF = random survival forest
sVTTC = solid venous tumor thrombus consistency
VTTC = venous tumor thrombus consistency

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Objectives: To evaluate the prognostic role of venous tumor thrombus consistency in patients with renal cell carcinoma.

Methods: A retrospective evaluation of the data of patients with renal cell carcinoma and a tumor thrombosis submitted to surgery from 2000 to 2013 was carried out. Histological slides were revised by two uropathologists, blinded of the clinical outcome, to assess venous tumor thrombus consistency classified as solid venous tumor thrombus consistency or friable venous tumor thrombus consistency. The statistical correlation between venous tumor thrombus consistency and other adverse features was assessed. Then the predictive ability of an integrated prognostic model, generated by Cox regression and random survival forest, was evaluated, with and without the inclusion of venous tumor thrombus consistency, by integrated Brier score, dynamic receiver operating characteristic curves, integrated discrimination improvement index and category-less net reclassification index.

Results: The data of 147 patients were analyzed, 79 with a solid venous tumor thrombus consistency and 68 with a friable venous tumor thrombus consistency, followed for a median period of 40.5 months. Venous tumor thrombus consistency was assessed with a high interobserver agreement (145/147 cases). The presence of a friable venous tumor thrombus consistency was associated with some adverse prognostic factors (symptoms, lymphnodal and distant metastasis, larger tumor diameter, higher cephalad thrombosis level, necrosis, microvascular invasion) and to a worse cancer-specific and overall survival at univariate analysis. However, venous tumor thrombus consistency was not predictive of survival, and did not improve the performance of a multivariable model that included a set of informative predictors.

Conclusion: Venous tumor thrombus consistency does not seem to have an independent prognostic role in patients with renal cell carcinoma.

Key words: consistency, prognosis, renal cancer, survival, thrombosis.

Introduction

The prognosis of RCC with tumor thrombosis is quite heterogeneous and not always predictable. Indeed, even if there are various prognostic factors generally effective for RCC, such as tumor size, grading, histological subtype, presence of sarcomatoid features, invasion of perirenal tissues and nodal or distant metastasis, as well as in the cases with a thrombosis, very few factors specific to these patients are available and their role is still controversial, as it is for the cranial level reached by the thrombus.[1–6]

Surgery in this setting is highly invasive and can be curative only in a subset of patients, so that a more precise prognostic prediction might be useful for surgical selection, indication to neoadjuvant or adjuvant therapy and follow up.

Recently, VTTC, defined as solid or friable, has been suggested as a prognostic factor by Bertini *et al.*; in that study, VTTC was independently related to survival, both OS and CSS, and was shown to slightly improve the predictive performances of a risk model.[7] At present, the only study that tried to validate the prognostic role of VTTC in an external setting achieved rather conflicting results, as VTTC was shown to be significantly associated only to OS and solely in patients without metastasis at diagnosis.[8]

Therefore, the prognostic role of VTTC still needs to be ascertained. The aim of the present study was to investigate if and to what extent it is an independent predictor of CSS and OS.

Methods

The data of all the patients submitted to surgery for RCC at Spedali Civili Hospital, Brescia, Italy, are stored in a prospectively-maintained database, which includes more than 2300 consecutive patients. After surgery, all the patients are followed according to a tailored protocol at a dedicated office.[9]

This database was used to retrieve the information of patients with RCC and tumor thrombosis observed in the period from 2000 to 2013. In lieu of formal ethics committee approval, the principles of the Helsinki declaration were followed.

The histological specimens were independently revised by two uropathologists. One was skilled, with more than 20 years of experience (RT), and the second was a novice, attending the last year of residency (MY); both were blinded to the clinical outcome of the patients. The revision assessed tumor size, histological subtype, Fuhrman grading, invasion of perirenal tissues, microvascular invasion, coagulative tumor necrosis and sarcomatoid de-differentiation, all defined according to the recommendations from the last consensus conference of the International Society of Urological Pathology.[10,11]

Following the definition used by Bertini *et al.*, VTTC was defined as solid when the thrombus appeared compact and cohesive, with a rounded linear profile and an endothelial lining simulating a pseudocapsule in more than 90% of its surface, otherwise it was defined as friable if it was incoherent, irregular, with necrotic areas and a fragmented aspect.[7] Furthermore, the extent of the friable pattern was defined limited if present in less than 50% of the specimen, and extensive when more represented (Fig. 1).

Statistical analysis

OS was calculated from the date of surgery to the date of death from any cause or last follow up; CSS was calculated from the date of surgery to the date of death from cancer-related cause or last follow up.

To investigate the added value of VTTC for the prediction of OS and CSS, the statistical analysis compared the predictive performances of the multivariable model including VTTC plus a set of predictive covariates ($Model_1$) to the same model without VTTC ($Model_0$). The models used in the aforementioned analysis were the traditional Cox regression and RSF, a novel non-parametric machine learning method that is less prone to overfit, handles non-linearity, collinearity and interactions between predictors.[12] The selection of the predictive covariates for OS and CSS were carried out by means of the stepwise backward method (for Cox regression) and the method of minimal-depth variable importance (for RSF).[13]

The predictive power of $Model_0$ and $Model_1$ models was then estimated and compared by three classes of statistical measures for censored data:

1 Prediction error curves and cumulative prediction error (i.e. Integrated Brier Score) using cross-validation and bootstrap methods; the null hypothesis of absence of an added predictive value of VTTC was tested by the van de Wiel test.[14]
2 Cumulative/dynamic time-dependent ROC curves, a generalization of the ROC methodology in the presence of censored data; the significance of differences between area under the ROC curves was investigated using the test proposed by Blanche *et al.*[15]
3 As ROC curves might not be sensitive enough to capture incremental improvements from a given predictor, some reclassification measures were evaluated: IDI, NRI[16,17] and median improvement in risk score.

Kaplan–Meier survival curves adjusted for potential confounders and the associated log–rank test were estimated using inverse probability weights.[18]

Statistical significance was defined as a P-value <0.05. Statistical analyses were carried out using R version 3.1.0[19] with pec, randomForestSRC, timeROC, survIDINRI and ipw packages.

Results

During the period of the study, 1238 patients were submitted to surgery for a renal tumor; among them, 189 had a RCC with a thrombosis, and for 147 (77.8%) the pathological specimens were available.

A sVTTC was identified in 79 cases (53.7%), a fVTTC in 68 cases (46.3%), limited in 26, extensive in 42. The diagnosis between pathologists was concordant in 145 out of 147 cases (98.6%) relative to the discrimination between sVTTC and fVTTC, and in 65 out of 67 (97.0%) for the discrimination between limited and extensive fVTTC.

Table 1 compares the characteristics of fVTTC with sVTTC patients. The distribution of demographic features and comorbidities did not differ significantly, whereas several clinical and pathological features, indicative of more advanced stage and higher aggressiveness, were more common in patients with a fVTTC.

The patients were followed for a median time of 40.5 months (range 1–215 months, interquartile range 14–78 months). At last follow up, 53 patients (35.1%) were alive without evidence

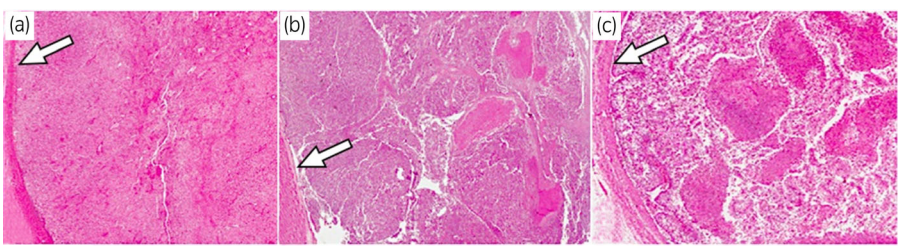

Fig. 1 Microscopic view of hematoxylin–eosin of (a) solid, (b) limited friable and (c) extensive friable tumor thrombus (the arrow indicates the venous wall).

Table 1 Patient characteristics and descriptive statistics in the overall study cohort and by VTTC

	All patients ($n = 147$)	Friable VTTC ($n = 68$)	Solid VTTC ($n = 79$)	P
Median age, years (range)	66.0 (35.5–85.0)	65.7 (37.0–79.3)	68.2 (35.5–85.0)	0.383
Sex, *n* (%)				0.733
Male	92/147 (62.6)	44/68 (64.7)	48/79 (60.8)	
Female	55/147 (37.4)	24/68 (35.3)	31/79 (39.2)	
Charlson Comorbidity Index, *n* (%)				0.616
0	93/147 (63.3)	45/68 (66.2)	48/79 (60.8)	
1–2	42/147 (28.6)	19/68 (27.9)	23/79 (29.1)	
≥3	12/147 (8.1)	4/68 (5.9)	8/79 (10.1)	
Symptoms, *n* (%)				0.013
Absent	46/146 (31.5)	13/67 (19.4)	33/79 (41.8)	
Local	67/146 (45.9)	35/67 (52.2)	32/79 (40.5)	
Systemic	33/146 (22.6)	19/67 (28.4)	14/79 (17.7)	
Side, *n* (%)				0.333
Right	75/147 (51.0)	38/68 (55.9)	37/79 (46.8)	
Left	64/147 (43.5)	28/68 (41.2)	36/79 (45.6)	
Bilateral	8/147 (5.5)	2/68 (2.9)	6/79 (7.6)	
Hystological subtype, *n* (%)				<0.001
Clear cell	130/147 (88.4)	53/68 (77.9)	77/79 (97.5)	
Others	17/147 (11.6)	15/68 (22.1)	2/79 (2.5)	
Median tumor diameter, cm (range)	8.0 (3.2–21.0)	9.0 (3.2–19.0)	8.0 (3.5–21.0)	0.042
Thrombosis level, *n* (%)				0.021
Renal vein	99/147 (67.3)	38/68 (55.9)	61/79 (77.2)	
Subdiaphragmatic inferior vena cava	37/147 (25.2)	23/68 (33.8)	14/79 (17.7)	
Supradiaphragmatic inferior vena cava/right atrium	11/147 (7.5)	7/68 (10.3)	4/79 (5.1)	
Perirenal tissues invasion, *n* (%)				0.067
Absent	42/147 (28.6)	14/68 (20.6)	28/79 (35.4)	
Present	105/147 (71.4)	54/68 (79.4)	51/79 (64.6)	
Nodal status, *n* (%)				0.029
pN0/Nx	127/147 (86.4)	54/68 (79.4)	73/79 (92.4)	
pN+	20/147 (13.6)	14/68 (20.6)	6/79 (7.6)	
Distant metastasis, *n* (%)				0.029
Absent	114/147 (77.6)	47/68 (69.1)	67/79 (84.8)	
Present	33/147 (22.4)	21/68 (30.9)	12/79 (15.2)	
Pathological grade, *n* (%)				<0.001
2	10/129 (7.7)	1/52 (1.9)	9/77 (11.7)	
3	58/129 (45.0)	16/52 (30.8)	42/77 (54.5)	
4	61/129 (47.3)	35/52 (67.3)	26/77 (33.8)	
Sarcomatoid differentiation, *n* (%)				1.000
Absent	121/147 (82.3)	56/68 (82.3)	65/79 (82.3)	
Present	26/147 (17.7)	12/68 (17.7)	14/79 (17.7)	
Microscopic necrosis, *n* (%)				<0.001
Absent	54/147 (36.7)	12/68 (17.6)	42/79 (53.2)	
Present	93/147 (63.3)	56/68 (82.4)	37/79 (46.8)	
Microvascular invasion, *n* (%)				0.075
Absent	46/147 (31.3)	16/68 (23.5)	30/79 (38.0)	
Present	101/147 (68.7)	52/68 (76.5)	49/79 (62.0)	

P-value of the Fisher's exact test (categorical variables) and of the Wilcoxon's rank-sum test (numerical variables).

of disease after a median time of 42.5 months from surgery, 36 (24.5%) were alive with a progression after a median time of 25.3 months, 52 (36.4%) died as a result of RCC at a median time of 25.5 months and six (4.1%) died from causes different from RCC at a median time of 23.0 months.

Table 2 reports the explanatory variables identified by two variable selection methods in the overall cohort and in the selected cohort of patients without metastasis at diagnosis. Adjusted HR for the selected covariates (age, thrombosis level, pathological grade, microvascular invasion, perirenal tissues invasion, Charlson Comorbidity Index and distant metastasis) were estimated for OS and CSS using a multivariable Cox model. It can be noted that VTTC did not show a statistically significant HR in all the analyses carried out (Table 2). Unadjusted HR are reported in Table S1.

In the overall cohort, the 5-year CSS (adjusted for other predictors) in patients with sVTTC and fVTTC was 61.0% (95% CI 49.9–74.7%) and 60.6% (95% CI 48.4–75.8%), respectively; the adjusted 5-year CSS for M0 patients with sVTTC and fVTTC was 69.0% (95% CI 57.7–82.5%) and 66.7% (95% CI 53.0–83.9%), respectively (Table 2). The comparison of the sVTTC- and fVTTC-adjusted survival

Table 2 Multivariable Cox regression analysis predicting OS and CSS in the overall cohort ($n = 147$) and in the M0 group ($n = 114$)

Variable	OS – all data (M0 and M1) HR (95% CI)	*P*	OS M0 group HR (95% CI)	*P*	CSS – all data (M0 and M1) HR (95% CI)	*P*	CSS M0 group HR (95% CI)	*P*
Age (years)								
Continuous variable	1.03 (1.00–1.06)	0.065	1.03 (0.99–1.08)	0.150	1.03 (1.00–1.06)	0.028	1.04 (0.99–1.08)	0.086
Thrombosis level								
Subdiaphragmatic inferior vena cava *vs* renal vein	2.37 (1.28–4.36)	0.006	3.41 (1.57–7.42)	0.002	2.39 (1.27–4.48)	0.006	3.73 (1.74–7.98)	0.001
Supradiaphragm. inferior vena cava/right atrium *vs* renal vein	2.09 (0.75–5.83)	0.159	6.94 (2.00–24.08)	0.002	1.60 (0.59–4.30)	0.354	4.07 (1.25–13.27)	0.020
Perirenal tissues invasion								
Present *vs* absent	3.21 (1.44–7.14)	0.004	4.42 (1.77–11.04)	0.001	2.36 (0.99–5.64)	0.053	3.68 (1.36–9.95)	0.010
Distant metastasis								
Present *vs* absent	4.97 (2.62–9.43)	<0.001	-	-	3.51 (1.79–6.88)	<0.001	-	-
Pathologic grade								
4 *vs* 2+3	3.02 (1.54–5.93)	0.001	1.95 (0.86–4.41)	0.108	2.68 (1.37–5.27)	0.004	1.63 (0.75–3.57)	0.220
Charlson Comorbidity Index, *n* (%)								
1–2 *vs* 0	2.15 (1.11–4.20)	0.024	1.84 (0.78–4.35)	0.165	-	-	-	-
≥3 *vs* 0	5.82 (1.77–19.17)	0.004	7.27 (2.03–25.99)	0.002	-	-	-	-
Microvascular invasion								
Present *vs* absent	-	-	-	-	1.93 (0.85–4.36)	0.115	2.68 (1.05–6.88)	0.040
Venous tumor thrombus consistency								
Friable *vs* solid	1.03 (0.54–1.97)	0.921	1.68 (0.74–3.79)	0.212	0.92 (0.48–1.76)	0.804	1.55 (0.72–3.32)	0.262
Estimated survival								
5-year survival (unadjusted)								
Solid	72.7% (62.5% - 84.6%)		79.2% (69.2% - 90.5%)		74.9% (64.8% - 86.7%)		80.6% (70.8% - 91.8%)	
Friable	47.0% (35.1% - 63.0%)		56.9% (42.7% - 75.8%)		51.4% (39.0% - 67.6%)		60.9% (46.6% - 79.7%)	
5-year survival (adjusted)								
Solid	59.0% (48.0% - 72.6%)		68.1% (56.8% - 81.7%)		61.0% (49.9% - 74.7%)		69.0% (57.7% - 82.5%)	
Friable	57.0% (45.6% - 71.3%)		63.7% (50.0% - 81.0%)		60.6% (48.4% - 75.8%)		66.7% (53.0% - 83.9%)	
10-year survival (unadjusted)								
Solid	69.8% (58.8% - 82.8%)		75.9% (64.8% - 88.9%)		71.9% (60.9% - 84.9%)		77.3% (66.2% - 90.1%)	
Friable	32.6% (21.0% - 50.5%)		40.6% (26,1% - 63.2%)		35.6% (23.3% - 54.6%)		43.5% (28.3% - 66.8%)	
10-year survival (adjusted)								
Solid	57.0% (45.6% - 71.3%)		65.7% (53.8% - 80.3%)		59.0% (47.4% - 73.5%)		66.6% (54.7% - 81.2%)	
Friable	41.3% (28.9% - 59.2%)		46.8% (32.0% - 68.3%)		44.2% (31.1% - 62.8%)		49.0% (33.8% - 71.1%)	

Unadjusted and adjusted estimated 5-year and 10-year survival with 95% confidence interval.

distributions by the log–rank test did not show significant differences (Fig. S1b,d). Similar results were found for OS (Fig. S1a,c).

An extensive analysis showed that VTTC, when used together with other informative variables, did not significantly improve the predictive value of two risk models for OS or CSS. The prediction error curves of models with and without VTTC, shown in Figure 2, are almost overlapping, and did not show a significant contribution of this covariate to the prediction of OS and CSS. This result was confirmed in Table S2, where two measures of predictivity (Integrated Brier Score and time-dependent area under the curve) and three reclassification measures (IDI, continuous-NRI and median improvement in risk score) for models with/without VTTC were compared; no statistically significant and clinically relevant differences were found.

Among patients with a fVTTC, the adjusted 5-year CSS in patients with extensive and limited fVTTC was 50.3% (95% CI 35.2–72.0%) and 64.2% (95% CI 45.8–90.0%), respectively; the adjusted 5-year CSS for M0 patients with extensive and limited fVTTC was 53.5% (95% CI 34.9–81.8%) and 87.1% (95% CI 71.9–100.0%), respectively. The comparison of sVTTC to extensive and limited fVTTC did not show significant differences in CSS curves (Fig. S2b,d). Similar results were found for OS (Fig. S2a,c).

Discussion

The present study reached four main findings. First, VTTC can be reliably assessed, with a high interobserver agreement between an expert and a novice pathologist, confirming that the diagnosis of this parameter is easy and reproducible.

Second, a fVTTC is indicative of an aggressive disease, because this pattern was strictly associated with some clinical and pathological features that are typical of the more advanced tumors – symptoms, lymphnodal and distant metastasis, larger diameter, higher cephalad thrombosis level, necrosis and microvascular invasion. This observation confirms what was reported by the two previous studies on VTTC, with comparable cohorts (147 *vs* 174 *vs* 184 patients) and median follow-up times (41 *vs* 24 *vs* 49 months).[7,8] It could be speculated that the higher clinical aggressiveness of fVTTC, shown by the association with many adverse clinical factors, could be attributed to a

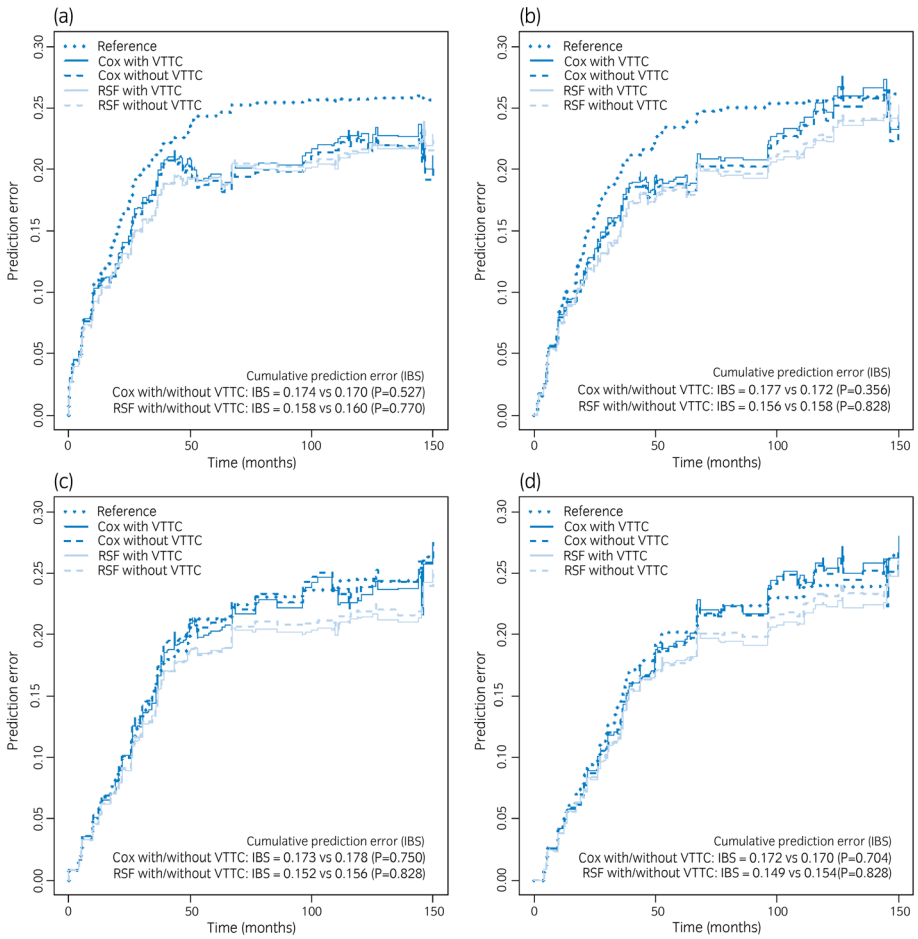

Fig. 2 Prediction error curves for Cox and RSF predictors with and without VTTC. (a) OS in the whole dataset. (b) CSS in the whole dataset. (c) OS in the M0 group. (d) CSS in the M0 group.

greater tendency to the spreading of the tumor facilitated by a lack of connective tissue and adhesion molecules that render less cohesive cancer cells.[8] In any case, the reliability and rapidity of diagnosis, and the relationship with various other pathological features make it advisable that VTTC should be reported by pathologists, as it could contribute to the definition of the biology of the disease, and indicate further investigations in cases with friable VTTC and unexpected favorable morphological aspects.

Third, VTTC was not a statistically significant and clinically relevant prognostic factor of survival when used together with other pathological and clinical predictors. On one hand, the univariate analysis showed that the presence of a fVTTC was significantly associated with a worse OS and CSS survival, in accordance with the two previous studies on VTTC.[7,8] It is noteworthy that the extension of the friable pattern (limited vs extensive) has a relationship with survival, even if without statistical significance. On the other hand, in contrast to previous studies, the association between VTTC and survival was not confirmed by multivariable analysis, and VTTC failed to significantly improve the predictive ability of models that include other informative variables, such as the level of thrombosis, perirenal tissue invasion, distant metastasis, high grading and Charlson index. On this point, some criticisms can be made of the two previous studies. Bertini *et al*. definitely stated that VTTC is a valuable independent prognostic factor, with respect to CSS and OS, in M0 and M1 cases; however, it should be noted that the additional predictive value of VTTC that they estimated was statistically significant, but of limited clinical value, being equal only to +2.5%.[7] Weiss *et al.* showed that VTTC is an adverse prognostic predictor only for OS and solely in M0 patients, whereas CSS was not assessed at all.[8] It is also noteworthy that they did not estimate any measure of predictivity for VTTC, and their analysis of OS was not adjusted for comorbidities, which in this setting are particularly relevant considering the age of the patients and the morbidity of the surgical procedures. Indeed, in our and in another study[20] the Charlson index is an independent predictor of OS. These data show that even if fVTTC is indicative of unfavorable biological behavior, its role in determining the prognosis is not relevant enough when other stronger prognostic factors are considered. Obviously, it cannot be excluded that in larger cohorts this effect could become more evident.

Finally, we observed that all the cases with a papillary subtype had a friable VTTC, and we suggested the hypothesis that the growth pattern of this histological subtype, typically with multiple papillae cannot be cohesive enough to appear solid. Indeed, also in the study of Weiss *et al.*, the papillary subtype had a fVTTC in 83% of cases, confirming our observation.[8] So, the chance that a thrombus could be classified as solid in this histological subtype should be better discussed, and VTTC should probably be reported only for clear cell RCC.

The main limitations of the present study were its retrospective design, limited sample size and the not negligible rate of cases for whom slides were not available.

In conclusion, the present study showed that VTTC can be reliably assessed, is strongly associated with several well-established adverse prognostic factors, but does not independently predict survival in patients with renal cancer and venous thrombosis.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1 Adjusted survival curves for sVTTC and fVTTC and for (a) OS and (b) CSS in the overall cohort (M0 and M1), and for (c) OS and (d) CSS in the M0.

Fig. S2 Adjusted survival curves for sVTTC and fVTTC and for (a) OS and (b) CSS in the overall cohort (M0 and M1), and for (OS) OS and (d) CSS in the M0.

Table S1 Unadjusted Cox regression analysis predicting OS and CSS in the overall cohort ($n = 147$, M0 and M1) and in the M0 group ($n = 114$); unadjusted and adjusted 5-year and 10-year survival with 95% confidence interval.

Table S2 Evaluation of the predictive power of venous tumor thrombus consistency for OS and CSS in the overall cohort (M0 and M1), and in the M0 group. The predictive powers of the models with and without VTC were evaluated and compared using the Integrated Brier Score and the time-dependent area under the ROC curve. The added discrimination offered by the addition of VTC to a predictive model was also evaluated using Integrated Discrimination Improvement, continuous Net Reclassification Improvement and the median improvement in risk score.