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Original paper

Tumour thrombus consistency has no impact on survival in patients with renal cell carcinoma

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The prognosis of renal cell carcinoma (RCC) with venous tumour thrombus (VTT) is variable and not always possible to predict. The prognostic impact and independence of tumour thrombus-related factors including the recently introduced tumour thrombus consistency (TTC) on overall survival remain controversial. The aim of this study was to investigate the prognostic role of TTC in patients' survival. We determined the tumour thrombus consistency (solid vs. friable) in a cohort of 84 patients with RCC and VTT who underwent nephrectomy with thrombectomy, and performed a retrospective evaluation of the patients' data from the prospectively maintained database. A total of 45% of patients had solid thrombus (sTT) and 55% had friable thrombus (fTT). The venous tumour thrombus consistency was not predictive of overall survival. Further studies, preferably prospective and with a larger number of patients, are needed to validate the obtained results, as well as to evaluate the usefulness of tumour thrombus consistency in clinical practice for stratifying the risk of recurrence and planning further follow-up.

Key words: renal cell carcinoma, tumour thrombus, consistency.

Introduction

Renal cell carcinoma (RCC) is one of the very few malignancies with an ability to extend into the venous system, and to form a tumour thrombus (TT) involving the renal vein (RV), inferior vena cava (IVC), or even the heart [1, 2]. The estimated VTT prevalence ranges between 4% and 36% of all RCC patients, and it is most commonly located within the RV [3, 4]. Although several prognostic clinicopathological features including tumour stage, grade, lymph node involvement, metastatic status, presence of necrosis and sarcomatoid differentiation have been identified for RCC patients with VTT, the importance of venous tumour thrombus consistency in this setting has not been well studied to date [5, 6, 7, 8, 9].

In fact, there have been only three studies in total that have investigated the significance of TT consistency for patients' survival, and they produced rather conflicting results [10, 11, 12]. To address this vacuum, we analysed the impact of tumour thrombus consistency on patients' survival.

Material and methods

This study was carried out in agreement with applicable laws and regulations, good clinical practice, and ethical principles, as described in the Declara-

tion of Helsinki of 1975, and revised in 2008. We retrospectively analysed 639 patients with renal cell carcinoma treated with partial, radical or cytoreductive nephrectomy at a single academic centre (2007-2015), from a prospectively maintained database. Of those, 84 patients had RCC with venous involvement. The records of these patients were reviewed for demographics, surgical details, tumour pathology, and oncological outcomes.

Preoperative assessment

The cranial extent of the VTT was defined as per the Neves and Zincke classification system [13]. The level of VTT was assessed in all cases with computed tomography (CT) or with magnetic resonance angiography and, in cases with cardiac involvement, additionally with transoesophageal echocardiography. The presence of synchronous chest metastases was evaluated with thoracic CT or chest X-rays, whereas bone scans and brain CT were performed when clinically indicated.

Surgery

None of our patients underwent neoadjuvant therapy for the cancer nor was embolised. All patients underwent radical or cytoreductive nephrectomy with thrombectomy. The surgical approach was determined by the cranial extent of the TT. For level 0 TT, a laparoscopic approach or flank incision was used, while for stages I-IV TT a chevron incision was performed. It was extended cephalad to include sternotomy when cardiopulmonary bypass was indicated or to mobilise the liver for suprahepatic IVC control. Cardiopulmonary bypass with moderate hypothermic cardiac arrest was performed in 22 cases.

Pathological findings

All microscopic studies were retrospectively reviewed by a single uropathologist blinded to the patient outcomes. All patients included in the current analysis had tumour thrombus tissue available for histological examination. The TNM staging was

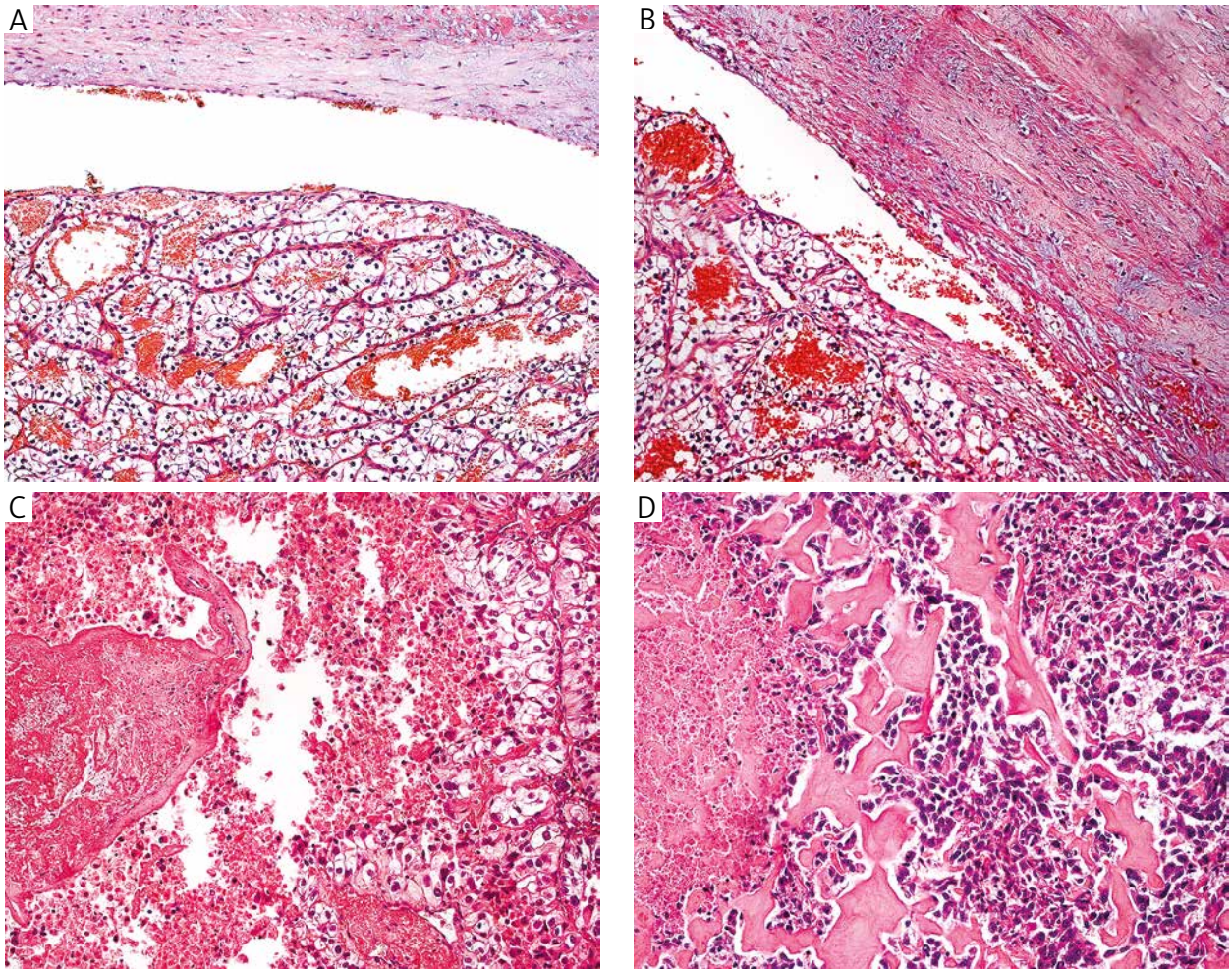

Fig. 1. Microscopic view of hematoxylin-eosin stain of a solid (A, B) and friable (C, D) venous tumour thrombus, objective magnification 20×

re-classified according to the 2009 Union for International Cancer Control/American Joint Committee on Cancer TNM staging system based on the histopathological report [14]. Where TNM was not clear, the histological slides were reassessed. The morphological aspect of the TT was classified into solid (sTT) or friable (fTT) according to the definition described by Bertini *et al*. [10]. Briefly, in solid TT, tumour growth was defined as compact and cohesive, with a rounded linear profile and an endothelial lining simulating a pseudocapsule (Fig. 1A, 1B). In friable TT, tumour cells were defined as intermingled with abundant necrosis and fibrin, with a scalloped, irregular profile and fragmented aspect, sometimes with thin papillary features (Fig. 1C, 1D). Finally, TT was classified as solid when at least 90% of the samples showed solid features.

Follow-up after surgery

The follow-up after surgery was performed at the discretion of the urologists and medical oncologists. The treatment recurrence differed among practitioners (metastasectomy and/or immunotherapy or targeted therapy) and was not considered in the analyses. Data on deaths in people with RCC and VTT were obtained from the Death Register of the Polish Ministry of Health and Social Welfare and from the Register of Births, Marriages and Deaths of the Polish Registry Office.

Statistics

Overall survival (OS) was calculated from the date of surgery to the date of death from any cause or last follow-up. The impact of TT consistency on the study variables was analysed using Student's t test and a test for two proportions. The associations between parameters were examined using Spearman's rank correlation coefficient and multiple logistic regression analyses. Survival curves were estimated using the Kaplan-Meier method, and differences among survival curves were tested using the log-rank test. A p value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using the statistical package SPSS for Windows (version 21; SPSS, Chicago, IL, USA).

Results

During the period of the study, a total of 84 patients with RCC and TT underwent radical or cytoreductive nephrectomy and tumour thrombectomy. The mean age in the entire group was 64.5 years (range: 26-84). There was a preponderance of men (59%), right tumours (64%), and clear cell RCC histological subtype (85%). The TT level 0 was in 33 patients (39%), level I in 10 (11%), level II in 14 (17%), level III in 9 (10%), and level IV in 17 (20%). Overall, 7% of patients had positive lymph nodes and 11% had distant metastases.

Of the 84 patients, 38 patients (45%) had solid TT, whereas friable TT was identified in 46 patients (55%). The distribution of demographic characteristics, as well as clinicopathological features, did not differ significantly between these two groups of TTs ($p < 0.05$). The clinicopathological characteristics of the entire cohort of patients, as well as of the two subcohorts of patients classified as per the TT consistency, are presented in Table I.

The median follow-up was 9 months (range: 1-66 months, interquartile range 3-20 months). At the last follow-up, 49 patients (58%) were alive without evidence of the disease, after a median time of 10 months from surgery. The median overall survival was 9 months. The median OS was 10 months for patients with solid thrombus, whereas it was 8 months for patients with friable TT. The comparison of sTT and fTT did not show significant differences in OS curves during the study period (Fig. 2). The p value for 1-, 2-, 3-, and 5-year OS in patients with sTT vs. fTT was 0.198, 0.251, 0.714, and 0.554, respectively.

In the univariate and multivariate analyses only Fuhrman grade and presence of distant metastases were statistically significant predictors of overall survival in patients with TT ($r = 0.235$, $p = 0.001$, and $r = 0.191$, $p = 0.006$, respectively). In contrast, tumour consistency (sTT vs. fTT), patients' age, gender, tumour side, pathological tumour stage, tumour thrombus level, lymph node involvement, histological tumour subtype, tumour necrosis, invasion of the venous wall by a thrombus, and tumour fat invasion were not found to impact survival in the current study.

Discussion

Despite many efforts in elucidating the impact of venous tumour thrombus on survival of patients with RCC, controversies surrounding this issue remain. While several clinicopathological features including cephalad extension of TT have been proposed as independent prognostic factors for patients' survival by some investigators, their role in that setting has not been confirmed by others and is still under debate [5, 6, 7, 8, 9].

Recently, three studies have investigated the effect of the venous tumour thrombus consistency on the postoperative survival in patients with RCC and TT [10, 11, 12]. Consistent with these studies, we retrospectively assessed the prognostic significance of thrombus consistency in a cohort of 84 patients with TT.

Table I. Patient characteristics and descriptive statistics

	All patients	Solid TT (n = 38)	Friable TT (n = 46)	p
Mean age, years, ±SD (range)	64.5 ±11.0 (26-84)	63.8 ±11.5 (26-84)	65.0 ±10.7 (26-84)	0.618
Sex, n (%)				
Male	50 (59.5%)	22 (57.9%)	28 (60.9%)	0.782
Female	34 (40.5%)	16 (42.1%)	18 (39.1%)	0.782
Side, n (%)				
Right	54 (64.3%)	28 (73.7%)	26 (56.5%)	0.102
Left	30 (34.7%)	10 (23.3%)	20 (43.5%)	0.102
TT level, n (%)				
0	33 (39.3%)	18 (47.4%)	15 (32.6%)	0.168
1	10 (11.9%)	5 (13.2%)	5 (10.9%)	0.747
2	14 (17.9%)	6 (15.8%)	9 (19.6%)	0.653
3	9 (10.7%)	4 (10.5%)	5 (10.9%)	0.960
4	17 (20.2%)	5 (13.2%)	12 (26.1%)	0.142
Histological subtype, n (%)				
Clear cell RCC	71 (85.5%)	34 (91.9%)	37 (80.4%)	0.254
Others	12 (14.5%)	3 (8.1%)	9 (19.6%)	0.128
Sarcomatoid features, n (%)				
	3 (3.6%)	2 (5.3%)	1 (2.2%)	0.448
Fuhrman grade, n (%)				
1+2	29 (34.5%)	19 (22.6%)	10 (11.9%)	0.07
3	37 (44.0%)	13 (34.2%)	24 (52.2%)	0.099
4	18 (21.4%)	6 (15.8%)	12 (26.1%)	0.252
Perinephric fat invasion, n (%)				
Yes	52 (61.9%)	21 (55.3%)	31 (67.4%)	0.255
No	32 (38.1%)	17 (44.7%)	15 (32.6%)	0.255
Tumour necrosis, n (%)				
Yes	31 (36.9%)	10 (26.3%)	21 (45.7%)	0.068
No	53 (63.1%)	28 (73.7%)	25 (54.3%)	0.068
Venous wall cancer invasion, n (%)				
Yes	(%)	15 (39.5%)	17 (37.0%)	0.813
No	(%)	23 (60.5%)	29 (63.0%)	0.813
Urinary collecting system invasion, n (%)				
Yes	13 (15.5%)	5 (13.2%)	8 (17.4%)	0.593
No	71 (84.5%)	33 (86.8%)	38 (82.8%)	0.593
pT stage, n (%)				
pT3a	43 (51.8%)	22 (59.5%)	21 (45.7%)	0.264
pT3b	20 (24.1%)	9 (24.3%)	11 (23.9%)	0.980
pT3c	14 (16.9%)	5 (13.5%)	9 (19.6%)	0.434
pT4	6 (7.2%)	1 (2.7%)	5 (10.9%)	0.144
Nodal status, n (%)				
pN0/cNo	76 (90.5%)	35 (92.1%)	41 (89.1%)	0.644
pN+	8 (9.5%)	3 (7.9%)	5 (10.9%)	0.644

Table I. Cont.

	All patients	Solid TT (n = 38)	Friable TT (n = 46)	p
Distant metastases, n (%)				
cM0	74 (88.1%)	34 (89.5%)	40 (87.0%)	0.723
cM1	10 (11.9%)	4 (10.5%)	6 (13.0%)	0.723

*TT – tumour thrombus; n – number of patients; SD – standard deviation; pT stage – pathological tumour stage; c – clinical; p – pathological; N – lymph nodes; M – distant metastases; * – statistically significant*

In the present study TTC was not a predictor of OS. Our findings are in concordance with the previous report by Antonelli *et al*., who found that thrombus consistency was not a statistically significant and clinically relevant prognostic factor for either OS or cancer-specific survival when used together with other pathological and clinical predictors [12].

However, our findings are in disagreement with the two earlier studies that suggested friable TT to be associated with worse prognosis [10, 11]. The observed differences regarding the predictive value of TTC among our and the aforementioned studies may be due to two main reasons. Firstly, there were marked differences in the number of patients with fTT vs. sTT among the studies. In our study, the fTT to sTT ratio was 1.22 and was close to the one reported by Antonelli *et al.* (0.85) [12], whereas in the study by Bertini *et al*. it was 0.15 [10], and in the analysis by Weiss *et al*. it was 0.63 [11]. The low proportion of fTT combined with the limited sample size could have had an effect on the results reported by the group of researchers led by Bertini and Weiss. Secondly, in the previous studies, the two subcohorts of patients with RCC and TT, i.e. patients with fTT and with sTT, had statistically different demographic as well as clinicopathological characteristics, including several potentially prognostic predictors (tumour grade, pathological stage, nodal status, distant metastases, tumour necrosis, TT level, and histological subtype), with adverse features dominating in the patients with fTT. The heterogeneity of the analysed groups of patients is a likely source of a selection bias and might have had an effect on the patients' survival.

Strengths and limitations of the study

Our study was a retrospective analysis of a limited number of patients and as such is subject to the bias and limitations inherent to this type of study. However, the data used in the analyses were obtained from a prospectively maintained database, which reduced the risk of errors and/or omissions. The two groups of patients were relatively homogeneous, and there were no differences in the baseline clinicopathological characteristics of the two groups of patients. The relatively short-term follow-up restricted to some extent our results. Moreover, we used only overall survival as the endpoint of our study, as the cause of death could not have been determined reliably in all patients, and hence cancer-specific survival would have been likely affected. However, it should be noted that OS is the gold standard for cancer clinical research and is considered the most reliable and preferred cancer endpoint [15].

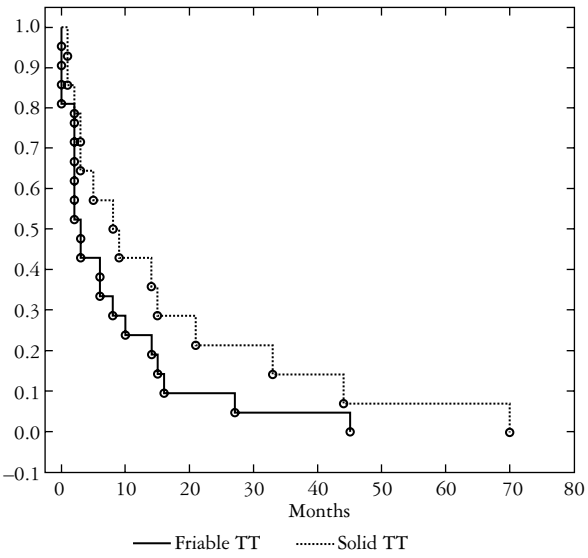

Fig. 2. Overall survival curves for patients with renal cell carcinoma and solid tumour thrombus or friable tumour thrombus extending into the venous system

In conclusion, this study showed that TTC does not predict survival in patients with renal cell carcinoma and venous tumour thrombus. Further studies, preferably prospective and with a larger number of patients, are needed to validate the obtained results, as well as to evaluate the usefulness of TTC in clinical practice for stratifying the risk of recurrence and planning follow-up.

The authors declare no conflicts of interest.

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