ORIGINAL ARTICLE

PROGNOSTIC SIGNIFICANCE OF TUMOUR THROMBUS CONSISTENCY ON CANCER-SPECIFIC SURVIVAL IN RENAL CELL CARCINOMA PATIENTS

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Background: Different studies have focused upon patients suffering from renal cell carcinoma (RCC) with inferior vena cava tumour thrombus. One biotic feature of renal RCC is venous system invasion. Both renal vein and inferior vena cava may be involved. The aim of current study was to evaluate the prognostic significance of the extent of thrombus in renal cell carcinoma patients with involvement of inferior vena cava. **Methods:** A total of 413 individuals were recruited in the study. All collected data were analysed retrospectively. Radical nephrectomy along with tumour thrombectomy was performed in all the participants. The pathological specimens were analysed for morphological feature, i.e., solid *vs* friable thrombus. To established clinicopathological predictor, Kaplan-Meier estimate and Cox regression analyses were done. **Results:** Friable and solid venous tumour thrombus (VTT) were found in 188 (46%) and 225 (54%) patients, respectively. For solid VTT, the Median Cancer Specific Survival (CSS) was 50 months while for friable VTT, the median CSS was 45 months. Thrombus consistency had no significant association with clinical features such as metastatic spread, pathological stage, perinephric fat invasion, and higher Fuhrman grade. Both survival analysis and Cox regression failed to be considered as a prognostic marker for CSS. **Conclusion:** Thrombus consistency appears not to be independently associated with survival in patients suffering from RCC.

Keywords: Renal cell carcinoma, survival, thrombus consistency, inferior vena cava

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INTRODUCTION

Renal cell carcinoma (RCC) of kidney occurs in both sexes in adult stage of life. RCC comprises 2–3% of all adult malignancies.[1] In the modern world the number of RCC patients is increasing by 2.5% annually. Since 2012, in Asian countries, about 121,000 patients with renal cancer were recorded. In Pakistan there is no authentic and reliable data available for the prevalence of RCC.[2] Most of the renal cancers are diagnosed incidentally. Amongst renal tumours, RCC constitutes the most frequent diagnosis, i.e., about 90% of total renal malagnancies.[3] Number of risk factors such as smoking, obesity, and hypertension are responsible for RCC disease.[4] RCC forms a venous tumour thrombus (VTT) which extends into the inferior vena cava (IVC) as well as into the renal vein.[5] RCC extension takes place in 4–10% of individuals suffering from it. RCC with VTT is associated with worse characteristics.[6] Venous migration and VTT formation are distinctive characteristics of RCC and is measured as an adverse prognostic factor for RCC.[7] In the current study, the aim of the study was to evaluate the prognostic significance of solid versus friable renal tumour thrombus (both renal vein and ICV thrombosis) with mean Cancer Specific Survival (CSS) in RCC patients in Peshawar.

SUBJECTS AND METHOD

A total of 413 patients were enrolled in our study who underwent radical nephrectomy and IVC tumour thrombectomy of solid or friable VTT came to Institute of Kidney Diseases, Peshawar. After surgery, follow-up of the enrolled patients was performed after every four months for the first year, every six months up to the 5th year and annually after that. Those patients with incomplete records of level of tumour thrombus, Fuhrmann grade, TNM (tumour, nodes, metastasis) staging and perinephric fat invasion (PFI) were excluded from the study. The patients were stratified based on their age and gender. By using the Bias software (epsilon, Frankfurt, Germany), all the collected data were analysed. The distribution of inferior vena cava tumour thrombus consistency in definite clinicopathological variables (pathological stage, VTT level, histological subtype, perinephric fat invasion, nodal status, distant metastasis, IVC wall invasion) were measured by means of Chi-square test. Tumour stages were categorised through Fuhrmann grade and was assessed by using Fisher's exact test. Survival analysis was performed by means of Kaplan–Meier analysis and all the variables were compared by means of log-rank test. The clinicopathologic variables were carefully chosen for assessment and their significance on cancer specific survival. Analyses (Univariable and multivariable) were done by means of Cox proportional

hazard regression model to evaluate the influence of variable on survival. All the performed tests were two sided, and $p<0.05$ was considered significant.

RESULTS

Our results show 54% patients with solid and 46% patients with friable tumour thrombus in the IVC. Of these patients, 215 were pN0/NxM0 while 28 and 170 patients were pN+M0 and pN+M+, respectively. The mean follow-up was 24 months and about 273 (66.1%) enrolled patients died due to RCC during our study period. Eighty-five (20.5%) patients were alive and were in disease-free state while 55 (13.4%) were alive but with distant cancer metastasis. The mean age of the study population was 61.5 years. The frequency of male patients was dominant over female patients and solid IVV VTT was more common than friable IVC VTT in both type of patients. The median CSS of patients with friable and solid thrombus, pathological stage as shown in Table-1. The pathological stage of each renal cell carcinoma sample was determined according to TNM (Tumour, Node, Metastasis) classification. The histological classification of tumour cells was performed as per Fuhrman nuclear grading system. As per Mayo VTT Classification, most of our patients fell into level I and II category (Table-2).

Table-1: Cancer Specific Survival of Patients

Thrombus consistency	No. of patients	Actuarial 5-yr CSS (%)	Median CSS (Months)	*p*
Friable	188	43.86	45	0.8
Solid	225	49.55	50	

Table-2: Characteristics of RCC patients with IVC TT [n (%)]

Variables	All patients	Friable IVC TT	Solid IVC TT	*p*
Patients	413	188 (46)	225 (54)	-
Median CSS		45	50	$p=0.8^a$
Pathological State				
pT3[b]	251 (60.76)	112 (27.12)	139 (33.66)	$p<0.001^a$
pT3[c]	130 (31.5)	61 (14.77)	69 (16.7)	
pT4	32 (7.74)	15 (3.63)	17 (4.12)	
Mean Value		188 (45.52)	225 (54.48)	
Fuhrman Nuclear Grade				
G1	9 (2.2)	4 (0.1)	5 (0.12)	$p<0.001^b$
G2	96 (23.25)	39 (9.4)	57 (13.8)	
G3	194 (47)	83 (20.1)	111 (26.88)	
G4	114 (27.6)	62 (15.01)	52 (12.6)	
Mean Value		44.6%	55.4 %	
VTT Level (Mayo classification)				
Level I	113 (27.4)	48 (42.48)	65 (57.52)	$p=0.03^a$
Level II	136 (33)	75 (55.15)	61 (44.85)	
Level III	85 (20.5)	37 (43.53)	48 (56.47)	
Level IV	79 (19.1)	28 (35.44)	51 (64.56)	
Mean Value		45.5%	54.5%	
Sex				
Male	278 (67.31)	123 (44.24)	155 (55.76)	$p=0.2^a$
Female	135 (32.69)	65 (48.15)	70 (51.85)	
Age				
Mean	61.5	61.0	61.9	$p=0.1^c$

a: Chi-square test, b: Fisher's exact test, c: *t*-test

Kaplan-Meier curves of cancer specific survival in individuals with friable and solid vena caval tumour thrombus are shown (Figure-1). Log-rank test shown no significant difference in cancer specific survival among individuals suffering from friable or solid IVC tumour thrombus (Table-3). The *p* of multivariable Cox regression analysis for histological subtype, nodal state and distant metastasis, perinephric fat invasion and IVC wall invasion fall in significant area (Table-4).

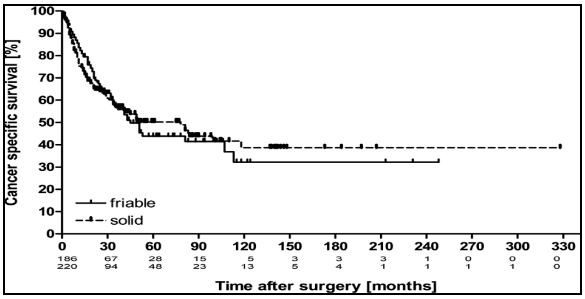

Figure-1: Kaplan-Meier estimates of cancer specific survival probability in patients with RCC and VTT involving the IVC stratified by thrombus consistency

Table-3: Kaplan-Meier estimates and log rank test

Patient at Risk	1-Year	3-Year	5-Year	*p*
Friable	58	45	15	>0.05
Solid	215	165	76	

Table-4: Multivariate Cox regression analyses predicting cancer specific survival in RCC patients (n=413)

Histological Subtype				
Clear cell RCC	371	169	202	$p<0.005$
Papillary RCC	29	11	18	
Chromophobe RCC	13	8	5	
Nodal State				
N0/Nx	297	134	163	$p<0.001$
N+	116	54	62	
Metastasis				
M0/Mx	303	145	158	$p<0.001$
M1	110	43	67	
Perinephric Fat Invasion				
Yes	266	124	142	$p<0.001$
No	147	64	83	
IVC Wall Invasion				
Yes	119	60	59	$p<0.01$
No	294	128	166	

DISCUSSION

Both RCC with VTT are life-threatening conditions and the treatment of RCC with vascular invasion is challenging and controversial. Surgical resection is found to be the best treatment procedure for therapy in non-metastatic disorders.[8,9]

The thrombus consistency (friable *vs* solid) in this study was non-significant to CSS. Patients with non-metastatic disease and friable VTT have higher-risk disease than patients with non-metastatic disease and solid VTT. A study by Antonelli[10] supports our results. This suggests that VTT consistency was not an

independent prognostic role in individuals suffering from RCC and no influence of thrombus consistency on CSS had been observed. Both solid and friable VTT showed altered features. In our subjects, poor outcome in individuals suffering from friable thrombus consistency has been found. Novara *et al* and Weiss *et al*, reported that individuals suffering from non-metastatic disorder and friable VTT had higher-risk disease than individuals suffering from non-metastatic disorder and solid VTT.[11,12] The pathological state (TNM classification) and Fuhrman grading of RCC samples also showed significant association with poor CSS. In individuals suffering from non-metastasized tumour, the Fuhrman grade and thrombus level were identified as independent predictors of poor survival representing the tumour's capability to spread aggressively.[13]

Upon multivariable analysis of overall survival (OS), friable thrombus consistency was found significant in non-metastasized individuals as previously observed by Vergho *et al*.[14] Tumour thrombus grade I and II clinically have shown significantly increased survival in comparison to grades III and IV, and thus proved the histological subtype as independent prognostic marker in non-metastasized individuals. Steffens *et al*[15] also showed that histological parameters of RCC influences the long-term prognosis in patients. Multivariate analysis of thrombus level with perinephric fat and IVC wall invasion showed significant association with poor CSS in RCC patients. These results were found to be similar to previous study by Bertini *et al*.[16]

CONCLUSION

Tumour Thrombus Consistency (friable or solid) has no prognostic significance on Cancer Specific Survival in patients with Renal Cell Carcinoma involving Inferior Vena Cava.

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