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Determinants of outcomes after resection of renal cell carcinoma with venous involvement

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Abstract
Purpose To determine the outcomes and to identify prognostic variables determining mortality and recurrence after surgery for renal cell cancer (RCC) with venous involvement.
Methods Retrospective evaluation of the medical records of 132 patients with RCC and tumor thrombi treated at Johns Hopkins Hospital (1997–2008) was done. Kaplan–Meier analysis was used to determine survivals. Uni- and multivariate Cox proportional analysis was done to identify predictors for recurrence, all-cause mortality (ACM) and cancer-specific mortality (CSM).
Results Mean follow-up was 30.3 (0.03–159.5) months. Sixty-four (48.5 %) patients had renal vein thrombus (Group 1), 55 (41.7 %) had subdiaphragmatic inferior vena cava (IVC) tumor thrombus (Group 2), while 13 (9.8 %) had involvement of IVC above diaphragm or atrial extension (Group 3). IVC thrombus was more common from the right-sided tumors. Patients with higher thrombus levels had more blood loss and complicated and longer hospital stay.Thrombus level was not found to be a predictor of recurrence, ACM and CSM. One- and three-year recurrence-free survivals for non-metastatic patients were 69 and 53 %. Tumor size ($p = 0.015$), grade ($p = 0.007$) and venous wall invasion ($p = 0.027$) were predictors for recurrence. Five-year overall survival was 48, 35 and 13 % for 3 groups, respectively. Presence of distant metastasis ($p = 0.032$), size ($p = 0.002$), histology ($p = 0.020$) and grade ($p = 0.013$) were predictors of ACM. Five-year cancer-specific survival was 65, 43 and 36 for 3 groups, respectively. Tumor size ($p = 0.001$) and distant metastasis at presentation ($p = 0.025$) were the predictors of CSM.
Conclusions Tumor thrombus level does not predict recurrence or mortality in RCC with venous involvement. Survival is determined by inherent aggressiveness of the cancer manifested by tumor size, grade and distant metastasis at presentation.

Keywords Nephrectomy · Renal cell cancer · Tumor thrombus · Venous involvement · Survival

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Introduction

Renal cell carcinoma (RCC) is the third most common urological malignancy. It is a highly vascular

neoplasm with tendency to invade the venous system resulting in tumor thrombus in the renal vein and/or inferior vena cava (IVC) in 4–10 % of the cases [1]. Unlike the vast majority of patients with renal masses, patients with venous involvement are often symptomatic either because of large tumor size causing flank pain and hematuria or because of tumor thrombus causing venous congestion and increased risk of embolism [2]. The most effective therapeutic option in patients with RCC and venous involvement is aggressive surgical resection, including radical nephrectomy and thrombectomy, even in the presence of metastases [3, 4]. The level of tumor thrombus dictates the surgical approach and invasiveness of the procedure; however, the role of tumor thrombus level as a predictor for prognosis in these patients has been debated. While some studies have shown better survival with only renal vein involvement compared to IVC thrombus [5–7], others have shown long-term outcomes to be independent of thrombus levels [4, 8, 9].

We hereby present a single institution review of patients with RCC and venous involvement with an aim to determine the oncological outcomes and to identify prognostic variables determining mortality and disease recurrence in this patient population.

Methods

After obtaining approval from the Institutional Review Board, a retrospective evaluation of the medical records of patients who underwent radical nephrectomy at Johns Hopkins Hospital between 1997 and 2008 was done. We identified 132 patients with RCC and venous involvement. Patients were divided into 3 groups according to level of venous involvement: Group 1 with tumor invasion limited to renal vein or its segmental muscle containing branches, Group 2 with IVC involvement below diaphragm and Group 3 with IVC involvement above diaphragm or atrial involvement. Patient demographics, tumor characteristics, peri-operative variables, complications and the course of the disease were studied. Histology subtype, determined according to Heidelberg classification, was split into clear cell and non-clear cell RCC. Complications were graded according to Clavien-Dindo classification of surgical complications [10] (data not shown).

Follow-up

Patients were followed up every 6–12 months. Physical examination, imaging (abdominal CT and chest X-ray) and laboratories were done at each follow-up. Disease recurrence was defined as detection of new suspicious lesion by imaging with or without biopsy confirmation. Disease progression was defined as increase in size and/or number of metastatic lesions on imaging. Patient's survival status was determined from medical records and social security death index registry. All-cause mortality (ACM) was defined as death from any cause. Cancer-specific mortality (CSM) was defined as death attributed to renal cancer in medical records. Survival was determined from the date of surgery to the date of last follow-up or death. Overall survival (OS) was defined as the interval from surgery to death from any cause. Cancer-specific survival (CSS) was defined as the interval from surgery to death from renal cancer.

Statistical analysis

Statistical analysis was done using statistical package for social sciences version 19 (Chicago, IL, USA). Kruskal–Wallis test or Mann–Whitney *U* test was run to compare means of continuous variables. Chi-square was run to compare proportions. Logistic regression analysis was done to identify predictors for complications. Uni- and multivariate Cox proportional hazard regression analysis was done to identify significant predictors of disease recurrence, ACM and CSM. OS and CSS were estimated and compared using Kaplan–Meier survival analysis. Statistical significance was considered at $p \leq 0.05$.

Results

The mean follow-up was 30.3 (0.03–159.5) months. Patent demographics, peri-operative variable and tumor characteristics are summarized in Table 1. Sixty-four (48.5 %) patients had renal vein thrombus (Group 1), 55 (41.7 %) had subdiaphragmatic inferior vena cava (IVC) tumor thrombus (Group 2), while 13 (9.8 %) had involvement of IVC above diaphragm or atrial extension (Group 3). IVC thrombus was more common from the right-sided tumors (82 %, $p < 0.001$). All 27 patients with distant metastasis had lung metastases, 3

Table 1 Patient demographics, peri-operative variables and tumor characteristics

	Renal vein ($n = 64$)	IVC below diaphragm ($n = 55$)	IVC above diaphragm ($n = 13$)	P value
Mean age at surgery (years)	63.9 (±11.9)	61.3 (±11.2)	64.6 (±10.6)	0.412
Gender				0.233
Male (%)	49 (76.6)	41 (74.5)	7 (53.8)	
Female (%)	15 (23.4)	14 (25.5)	6 (46.2)	
Side				<0.001
Left (%)	40 (62.5)	11 (20.0)	1 (7.7)	
Right (%)	24 (37.5)	44 (80.0)	12 (92.3)	
Distant metastases				0.007
Yes (%)	9 (14.1)	18 (32.7)	0 (0.0)	
No (%)	55 (85.9)	37 (67.3)	13 (100.0)	
Peri-operative course				
Approach				<0.001
Open (%)	30 (46.9)	53 (96.4)	13 (100.0)	
Lap (%)	34 (53.1)	2 (3.6)	0 (0.0)	
Surgery				
Radical nephrectomy alone (%)	49 (76.6)	0 (0)	0 (0)	
Radical nephrectomy and thrombectomy (%)	15 (23.5)	37 (67.3)	8 (61.5)	
Radical nephrectomy, thrombectomy, IVC excision and primary closure (%)	0 (0.0)	7 (12.7)	2 (15.4)	
Radical nephrectomy, thrombectomy, IVC excision and graft/patch repair (%)	0 (0.0)	11 (20.0)	3 (23.1)	
Cardiopulmonary bypass (%)	0 (0.0)	7 (38.9)	11 (84.6)	<0.001
Mean cardiopulmonary bypass time (min)	–	98.2 (±59.8)	128.8 (±48.1)	0.420
Mean estimated blood loss (ml)	526.3 (±608.5)	2820.3 (±3824.0)	3766.7 (±5409.6)	<0.001
No. of patient with early complications (%)	12 (18.8)	18 (32.7)	8 (61.5)	0.006
Post-op death (%)	1 (1.6)	2 (3.6)	2 (15.4)	0.059
Complications (n)				
	Arrhythmia (1)	Arrhythmia (2)	Arrhythmia (5)	
	Cerebrovascular accident (1)	Cerebrovascular accident (1)	Thromboembolic (2)	
	Ileus (2)	Thromboembolic (7)	Hemorrhage (1)	
	Thromboembolic (1)	Hemorrhage (7)	Multiorgan failure (1)	
	Hemorrhage (2)	Pneumonia (1)	Miscellaneous (1)	
	Wound dehiscence (1)	Miscellaneous (5)		
	Lymphocele (1)			
	Pneumonia (1)			
	Empyema (1)			
	Miscellaneous (2)			
Median hospital stay (days)	4.0	6.0	8.0	<0.001
Range	1–54	2–16	4–15	
Pathology				
Mean tumor size (±SD)	8.7 (±3.8)	10.7 (±4.1)	10.1 (±4.2)	0.03

Table 1 continued

	Renal vein ($n = 64$)	IVC below diaphragm ($n = 55$)	IVC above diaphragm ($n = 13$)	P value
Histology ($n = 131$)				0.426
Pure clear cell RCC (%)	56 (87.5)	43 (79.6)	10 (76.9)	
Other	8 (12.5)	11 (20.4)	3 (23.1)	
Fuhrman grade ($n = 130$)				0.232
1 (%)	0 (0.0)	1 (1.9)	0 (0.0)	
2 (%)	18 (28.1)	7 (13.2)	3 (23.1)	
3 (%)	34 (53.1)	26 (49.1)	6 (46.2)	
4 (%)	12 (18.8)	19 (35.8)	4 (30.8)	
Peri-nephric fat invasion ($n = 74$)				0.200
Positive (%)	19 (55.9)	26 (76.5)	4 (66.7)	
Negative (%)	15 (44.1)	8 (23.5)	2 (33.1)	
Adrenal gland invasion ($n = 93$)				0.634
Positive (%)	4 (9.8)	3 (6.7)	0 (0.0)	
Negative (%)	37 (90.2)	42 (93.3)	7 (100.0)	
Venous wall invasion ($n = 123$)				<0.001
Positive (%)	13 (21.7)	32 (62.7)	10 (83.3)	
Negative (%)	47 (78.3)	19 (37.3)	2 (16.7)	
Lymph nodes involvement ($n = 40$)				0.137
Positive (%)	8 (44.4)	6 (30.0)	2 (100.0)	
Negative (%)	10 (55.6)	14 (70.0)	0 (0.0)	

patients had bone, 2 had liver and 1 each had breast and retroperitoneal metastatic implant.

Patients with renal vein involvement had a smaller tumor size compared to patients with IVC thrombus ($p = 0.009$). No difference in tumor size was seen between Group 2 and 3. Tumor size was correlated with intra-operative blood loss ($p < 0.001$), tumor grade ($p < 0.001$) and venous wall invasion ($p = 0.006$).

Peri-operative period

Group 1 patients who underwent laparoscopic nephrectomy had smaller mean tumor size (7.5 vs 10.1 cm, $p = 0.008$), lesser mean intra-operative blood loss (249 vs 865 ml, $p = 0.001$) and shorter hospital stay (3.5 vs 7.0, $p < 0.001$) compared to open approach.

Complications during hospital stay were reported in 34.8 % of the procedures. Patients with higher thrombus levels had more intra-operative blood loss and had more complicated and longer hospital stay (Table 1). On logistic regression, thrombus level was the sole predictor for significant complications (grade 2–5) ($p = 0.002$, HR = 2.69 95 % CI = 1.45–4.98). There were no intra-operative deaths. Five deaths were reported in peri-operative period. One patient developed bilateral pulmonary embolism and was started on heparin, subsequently had extensive hemorrhagic stroke resulting in death. Refractory hemorrhage, multiorgan failure, cardiac arrest (unknown etiology) and metabolic acidosis secondary to bilateral iliac

Table 2 Overall and cancer-specific survival rates after surgery for renal cell cancer with venous involvement

	Overall survival		Cancer-specific survival	
	Three-year survival (±SE)	Five-year survival (±SE)	Three-year survival (±SE)	Five-year survival (±SE)
Whole cohort	50 (±5) %	38 (±6) %	62 (±6) %	52 (±7) %
Level of vein involvement				
Renal vein (Group 1)	56 (±7) %	48 (±9) %	65 (±8) %	65 (±8) %
IVC below diaphragm (Group 2)	44 (±7) %	35 (±7) %	55 (±9) %	43 (±10) %
IVC above diaphragm (Group 3)	40 (±15) %	13 (±12) %	71 (±18) %	36 (±27) %
Presence of distant metastasis at presentation				
Non-metastatic	56 (±5) %	43 (±7) %	68 (±6) %	58 (±8) %
Metastatic	28 (±9) %	22 (±9) %	39 (±12) %	28 (±13) %

artery thrombosis were listed as the reasons of death for the other 4 patients.

Disease recurrence and progression

During the follow-up period, 21 (80.8 %, excluding 1 post-op death) patients with distant metastasis progressed and 39 (38.6 %, excluding 4 post-operative deaths) patients without metastasis had disease recurrence (local or distant). One- and three-year recurrence-free survivals for non-metastatic patients were 69 (±5) and 53 (±6) %. One- and three-year progression-free survivals for patients with metastatic disease at presentation were 15 (±8) and 5 (±5) %. Patients with metastatic disease at presentation were more likely to experience disease progression than disease recurrence in non-metastatic patients ($p < 0.001$). While no predictors for progression were identified in patients with metastatic disease, tumor size ($p = 0.015$, HR = 1.10, 95 % CI = 1.02–1.18), tumor grade ($p = 0.007$, HR = 1.86, 95 % CI = 1.19–2.91) and venous wall invasion ($p = 0.027$, HR = 2.14, 95 % CI = 1.09–4.22) were predictors for disease recurrence in non-metastatic disease. On multivariate analysis, only tumor size ($p = 0.018$) was found to be a significant factor dictating recurrence.

All-cause mortality and overall survival

Twenty-six (40 %), 39 (70.9 %) and 10 (76.9 %) patients of the Group 1–3 patients, respectively, died by the time of conclusion of study period. Overall survivals of different groups are listed in Table 2. Patient with only renal vein involvement survived longer than patient with IVC thrombus (Gr. 1 vs Gr. 2 $p = 0.050$, Gr. 1 vs Gr. 3 $p = 0.025$). No difference in survival was seen in Group 2 and 3 ($p = 0.323$). Overall survival in patients with metastatic disease at presentation was shorter than patients with non-metastatic disease ($p = 0.030$ by log rank test, $p = 0.054$ by generalized Wilcoxon test). Overall survival curves are depicted in Fig. 1.

On univariate analysis, presence of distant metastasis ($p = 0.032$, HR = 1.75, 95 % CI = 1.05–2.91), tumor size ($p = 0.002$, HR = 1.10, 95 % CI = 1.03–1.17), histology ($p = 0.020$, HR = 1.91, 95 % CI = 1.11–3.31) and tumor grade ($p = 0.013$, HR = 1.53, 95 % CI = 1.10–2.13) were found to be significant predictors for all-cause mortality. On multivariate analysis, tumor size ($p = 0.001$) and non-clear cell histology ($p = 0.022$) were found to be independent predictors.

Cancer-specific mortality and survival

Out of the 52 patients, for whom information on reason of death was available, 37 (71.2 %) patients died of renal cancer, 14 (24.1 %), 19 (47.5 %) and 4 (36.4 %) in Group 1, 2 and 3, respectively. Cancer-specific survivals of different groups are listed in Table 2. No difference in cancer-specific survivals was found between groups with different level of thrombus. Patients with metastatic disease at presentation had shorter cancer-specific survival compared to non-metastatic patients ($p = 0.015$ by log rank test,

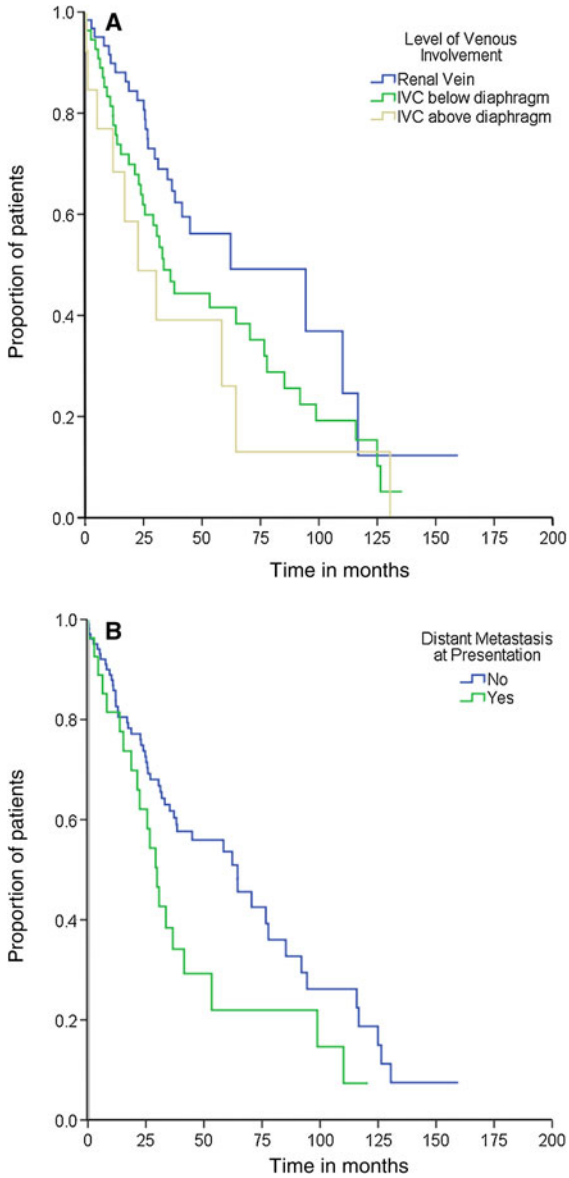

Fig. 1 Overall survival curves stratified according to **a** different levels of venous thrombus (Gr. 1 vs Gr. 2 $p = 0.050$, Gr. 1 vs Gr. 3 $p = 0.025$, Gr. 2 vs Gr. 3 = 0.323), **b** presence of distant metastasis at presentation ($p = 0.030$)

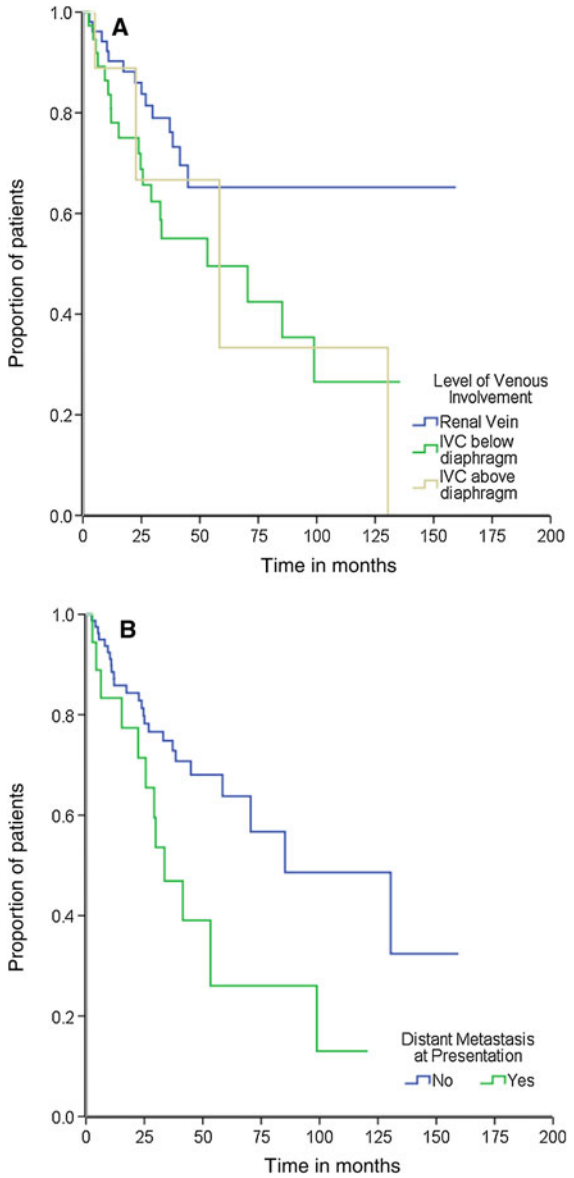

Fig. 2 Cancer-specific survival curves stratified according to **a** different levels of venous involvement (Gr. 1 vs Gr. 2 $p = 0.069$, Gr. 1 vs Gr. 3 $p = 0.623$, Gr. 2 vs Gr. 3 = 0.703), **b** presence of distant metastasis at presentation ($p = 0.015$)

$p = 0.053$ by generalized Wilcoxon test). Cancer-specific survival curves are depicted in Fig. 2. On uni- and multivariate Cox regression analysis, tumor size ($p = 0.001$, HR = 1.16, 95 % CI = 1.07–1.27) and distant metastasis at presentation ($p = 0.025$, HR = 2.22, 95 % CI = 1.11–4.45) were found to be significant predictors of cancer-specific death.

Comment

In patients with renal cancer and venous involvement, aggressive surgical resection remains a mainstay of therapy and ensures reasonable long-term survival [1–4, 11, 12]. Surgical resection is done for curative intent in non-metastatic patients, while in the presence of

distant metastasis, surgical resection is recommended for cytoreduction and/or palliation of symptoms [13–15]. The aim of current study is to study outcomes and identify prognostic variables after surgical treatment for renal cell cancer with venous involvement.

Five-year overall survival rate for non-metastatic patients in our cohort is 43 %. Five-year survival rates after radical nephrectomy and thrombectomy for the same group reported in literature varies from 34 to 72 % [2, 11, 16]. The wide variation in reported outcomes could be secondary to varied pre-operative assessment, surgical era, tumor biology, comorbidities of patient population and improvements in adjuvant therapy. In our study, patients with only renal vein involvement have better overall survival than patients with IVC thrombus. No difference in overall survival was seen according to level of IVC involvement. These results are similar to findings reported by Wagner et al. [6] from analysis of a multicenter study. Others have also not found proximal extent of thrombus to determine overall survival [8, 17]. In contrast, a recent analysis from multicentre study involving 1122 patients revealed survival rates to be different between renal vein, IVC below diaphragm and IVC above diaphragm involvement [18].

Five-year cancer-specific survivals for non-metastatic and metastatic renal cancer with tumor thrombus described in literature are 40–65 % and 6.5–28 %, respectively [15]. Our cancer-specific outcomes are toward higher limits of the range probably secondary to increased effectiveness of adjuvant therapy in current era. In our study, the five-year cancer-specific survival rates decrease with cranial extent of tumor but the difference was not statistically significant. In contrast, Dr. Blute's group from Mayo Clinic found significantly longer cancer-specific survival in patient with only renal vein involvement compared to IVC thrombus [19–21]. The prognostic value of thrombus level, however, remains controversial. We did not find tumor thrombus level to be a predictor for disease recurrence or survival similar to findings of Klatte et al., Wagner et al. and others [6, 16, 17], while Klaver et al. [22] and Martinez-Salamanca et al. [18] have found thrombus level to be an independent predictor for cancer-specific survival.

Seventy-five patients died during the follow-up period. On univariate analysis, tumor grade, size, histology and presence of distant metastasis were significant predictors of all-cause mortality which correlates with findings of other studies [6, 8, 18]. Only size and non-clear cell histology was significant on multivariate analysis. In our study, tumor size, not the Fuhrman grade, was an independent predictor similar to the studies by Wagner et al. and Parekh et al. [6, 8], while other studies have found tumor grade to independently determine overall survival [18, 23, 24]. Our results could be explained by presence of strong correlations between the tumor size and grade. Tumor size was also an independent predictor of cancer-specific death.

The other important factor determining cancer death was presence of distant metastasis at presentation. Patients with metastatic disease at presentation had significantly shorter overall and cancer-specific survival compared to rest of cohort. This result is in conformity with the literature [3, 6, 20, 25]. In addition, the most common cause of death after surgical resection in these patients is metastatic RCC as reflected by our results and findings from other studies.

Presence of lymph nodes involvement was found to be another independent prognostic factor determining survival in some studies [6, 16]. Since lymphadenectomy was not routinely performed, pathological data on lymph node involvement were present in only 40 patients with 16 of them positive for cancer. Presence of lymph node disease was not found to be a significant factor determining survival in our analysis, similar to results published by Montie et al. [25].

The importance of tumor fat invasion as a predictor for cancer-specific mortality in renal cancer with tumor thrombus has recently been described [16, 20, 21, 26]. These studies have demonstrated fat invasion by tumor as a poor prognostic variable. Also, some studies have demonstrated venous wall invasion to be an important prognostic variable [6, 17, 27]. Our study did not find peri-nephric fat or venous wall invasion to be a predictor of survival.

Tumor grade, size and venous wall invasion predicted disease recurrence in our patients. Tumor size was found to be the only independent factor determining disease recurrence. Again the strong correlation between the three factors explains only the tumor size to be an independent predictor. While the three-year recurrence-free survival for non-metastatic patients was 53 %, the progression-free survival for patients with metastatic disease was only 5 %, highlighting the fact that patients with metastatic disease at presentation have more aggressive cancer.

We report a peri-operative mortality 1.6 % in RV group and 5.9 % in IVC thrombus group which has been comparable to other contemporary studies [6, 8, 19]. The difference between peri-operative mortality between renal vein versus IVC thrombus was not significant. Bleeding and thromboembolism complications were the most common in our cohort. Early surgical complications were associated with higher thrombus level with rate as high as 61 % in patients with supra-diaphragmatic IVC thrombus. These findings are similar to the results reported by Blute et al. and Klatte et al. [16, 19].

The study is limited by retrospective analysis of outcomes of a single institution and small sample size. By limiting the study period to 10 years, we have tried to minimize the variability introduced by changes in pre-operative assessment, surgical technique and post-operative care in these patients. Also, some of our patients had received neoadjuvant and/or adjuvant immunotherapy at different stages in their disease course which might have affected survival rates in an unpredictable fashion.

Conclusion

Patients with RCC and venous involvement usually have bigger tumors and are symptomatic at presentation; therefore, aggressive surgical resection is warranted for palliation of symptoms and cancer control. Characteristics of primary tumor including tumor size, grade and presence of distant metastasis at presentation were predictors of cancer-specific survival in this cohort. Thrombus level was not a significant predictor for recurrence and survival but predicted the risk of complicated and prolonged hospital stay.

Conflict of interest The authors declare that there is no conflict of interest.

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