Original Article

Experience with management of renal cell carcinoma with inferior vena cava/right atrial tumor thrombus

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ABSTRACT

Introduction: We aimed to present our experience in managing renal cell carcinoma (RCC) with inferior vena cava (IVC) thrombus.

Methods: Records of all patients aged 18 years and older, with a diagnosis of primary renal masses with IVC thrombus, presenting to our institute from January 2012 to August 2020 were retrospectively reviewed. Patients with tumor thrombus limited only to renal vein were excluded from the analysis. Their hospital course and outcomes were recorded and evaluated for predictors of survival.

Results: During the study period, we treated 61 patients with a renal mass and concurrent IVC thrombus and 56 of these underwent surgery. 7 of them had level III and 6 had level IV thrombus. A total of six patients received neoadjuvant tyrosine kinase inhibitor (TKI) therapy and all of them showed a decrease in size and level of tumor thrombus and cardiopulmonary bypass was safely avoided. Fourteen patients had distant metastasis and underwent cytoreductive surgery and of these 12 patients received TKI therapy after surgery with a mean survival of 26.8 months. The overall survival at 2 and 5 years of nonmetastatic group was 81.1% and 47.5% respectively and in metastatic group was 35.1% and 0%, respectively. Poor performance status, distant metastasis, higher T stage, higher thrombus levels, and positive surgical margins were all predictors of decreased survival.

Conclusions: Complete surgical resection in both nonmetastatic and metastatic RCC with IVC thrombus has long-term survival benefits. Neoadjuvant TKI therapy, with adequate preoperative planning, helps in decreasing the size of the thrombus and in safely avoiding bypass in level III and IV IVC thrombi.

INTRODUCTION

Renal cell carcinoma (RCC) is the third most common malignancy of the genitourinary tract.[1] It is the commonest upper tract tumor showing extension of tumor thrombus into the renal vein and inferior vena cava (IVC). Tumour thrombus is found in about 4%–10% of patients with RCC,[2,3] and is more common in right-sided renal masses. The Mayo classification system is commonly used for classifying the level of IVC tumor thrombus.[4] The TNM classification (AJCC 8th Edition; 2017) is generally used for staging and surgical planning. Contrast-enhanced computer tomography (CECT) is the most common radiological investigation performed during the initial evaluation of RCC. However, on the identification of an IVC tumor thrombus, it is prudent to do a magnetic resonance imaging (MRI) preferably with venography, because MRI is the gold standard investigation for identifying any IVC wall invasion by the thrombus[5]

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which may necessitate a change of surgical planning. A significant proportion of patients present with unresectable or metastatic disease along with IVC thrombus. Among all options for treatment, surgical removal of the kidney along with IVC thrombectomy is the most beneficial, with 5-year survival rates varying from 50% to 65%.[6-8] When nephrectomy without IVC thrombectomy is done, the prognosis is extremely poor.[9] The procedure is technically difficult and requires multidisciplinary management. Even then, mortality has been reported to vary from 3% to 16% and morbidity can be up to 70%.[3,4,7] In this study, we have reviewed our series of cases and have presented our experience in management and outcomes.

MATERIALS AND METHODS

We retrospectively reviewed the records of all patients of RCC at our institute from January 2012 to August 2020. All patients aged 18 years and older, with a diagnosis of primary renal masses with IVC thrombus, were included in the analysis. Patients with tumor thrombus limited only to renal vein were excluded from the analysis. Data were recorded regarding symptoms, clinical findings, preoperative investigations, neoadjuvant therapy, need for added procedures such as angioembolization, intra-operative procedure and findings, tumor pathology, postoperative course, and duration of the last follow-up. The level of thrombus was classified as per the Mayo Clinic classification after evaluation by CECT and/or MRI of the abdomen with Doppler ultrasonography of the IVC in select cases. Complications that occurred during the same hospital stay or within one month of surgery were recorded and graded according to Clavien–Dindo grading. Follow-up time was calculated from the time of surgery until the death of the patient or the time of the last follow-up visit. The comparison of different parameters was done by Chi-square or Fisher's exact tests. Survival analysis was done by the Kaplan–Meier technique with the help of IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

During the study, there were 1309 patients presenting to the outpatient department with a diagnosis of renal mass due to RCC. There were 61 patients with concurrent IVC thrombus and 56 of these patients underwent IVC thrombectomy at the time of nephrectomy [Figure 1]. Of the remaining five patients, two were lost to follow up, one patient with a level IV thrombus developed massive pulmonary thromboembolism (PTE) 1 day prior to surgery and died. The remaining two patients were considered to have unresectable primary tumor due to involvement of the head of pancreas and the duodenum and superior mesenteric artery respectively. The baseline characteristics of those that underwent surgery and preoperative parameters are mentioned in Table 1.

A total of six patients received neoadjuvant tyrosine kinase inhibitor (TKI) therapy. Three patients had level III thrombus and 3 had level IV. Among the level III thrombi, the indication of neoadjuvant therapy was poor performance status in one case and tumor extension into confluence of hepatic veins in 2 cases. The first patient showed improvement in performance status after 3 months of sunitinib therapy and underwent open radical nephrectomy and IVC thrombectomy. The other two patients showed regression of the thrombus from the hepatic vein confluence along with a decrease in the diameter and vascularity of the thrombus as evidenced from the follow-up CECT scans, after 3 months of pazopanib therapy. One of the patients with level IV thrombi had thrombus extending to just below the level of the right atrium with extension into the confluence of the hepatic veins and also the opposite left renal vein. He showed a good response to pazopanib therapy and after 6 months, his thrombus had decreased in size to just above the diaphragm and had regressed from the left renal vein and the hepatic vein confluence. This patient underwent surgery without the need for sternotomy or cardiopulmonary bypass. The remaining 2 level IV thrombi also showed a similar response to TKI therapy with decrease in the level of thrombi and could avoid cardiopulmonary bypass during surgery. The mean duration of TKI therapy was 5.8 months (1–12 months) and three patients suffered from adverse effect in the form of oral ulcerations and gastric intolerance. A total of 14 patients (MSKCC risk classification: Favourable-2, Intermediate-12) had distant metastasis and underwent cytoreductive surgery. Ten patients had pulmonary, two had skeletal and one each had liver with pulmonary and skeletal with pulmonary metastases. Five patients underwent preoperative angioembolization for large vascular primary tumors.

Intraoperative findings are mentioned in Table 2. A total of 7 cases required sternotomy. Two of these were in level III thrombi where it was difficult to apply supra-hepatic clamp from the abdominal side due to the large diameter of the distended IVC. IVC wall invasion was seen in 11 patients and 3 of these required repair of the IVC wall using pericardial patch graft. The other 8 were managed by primary closure of the IVC using poly-propylene sutures. Lymphadenopathy was suspected in 19 patients with the help of preoperative imaging. Intraoperatively enlarged and suspicious lymph nodes isolated from the renal mass were found in only 14 patients in whom lymphadenectomy was performed. In the rest, lymphatic tissues were removed in toto with the primary mass. Additional organ resection like distal pancreatectomy with splenectomy, segmental transverse colon resection, and only splenectomy was required in three patients.

Postoperative outcomes have been shown in Table 3. The most common postoperative complications were nausea, vomiting, and fever. A total of 28 patients showed 30

Table 1: Baseline clinical characteristics and preoperative parameters

Baseline parameters	Total, *n* (%)	Level I	Level II	Level III	Level IV
Gender					
Male	48 (85.7)	18	18	6	6
Female	8 (14.3)	5	2	1	0
Total (*n*)	56	23	20	7	6
Age (mean±SD)	60±10.2	60±9.5	57±12	64±3.5	67±5.3
Symptoms at presentation					
Pain	23 (41.1)	7	9	5	2
Hematuria	31 (55.4)	11	14	4	2
Flank mass	4 (7.1)	1	3	0	0
Systemic symptoms	10 (17.9)	4	2	1	3
Disease side					
Left	21 (37.5)	11	5	4	1
Right	35 (62.5)	12	15	3	5
Maximum tumour diameter (cm), mean±SD	10±4	8.6±2.5	10.8±5	12±4.1	12.8±1.3
Distant metastases (on imaging)	14 (25)	5	5	4	0
Neoadjuvant targeted therapy					
Pazopanib	5 (8.9)	0	0	2	3
Sunitinib	1 (1.8)	0	0	1	0
Preoperative angioembolisation	5 (8.9)	0	1	2	2

SD=Standard deviation

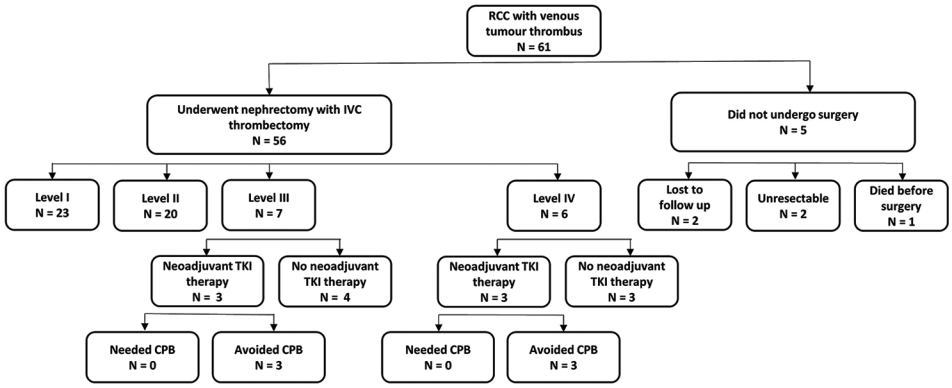

Figure 1: Flowchart showing distribution of cases

complications which were graded as per Clavien Dindo scoring system. Majority of the complications were Grade I. Two patients died in the immediate postoperative period. Of these, one patient had a level III thrombus and had needed extensive liver mobilization and a sternotomy for suprahepatic clamping. He developed diffuse oozing from the liver surface intraoperatively, requiring multiple transfusions and hepatic packing. Postoperatively, he went into shock and could not be revived. The other patient had a level IV thrombus, that was inside the right atrium. A fragment of this thrombus migrated into the pulmonary circulation causing PTE intraoperatively. Postoperatively, this patient could not be extubated and died from complications of PTE. The findings of pathological staging are outlined in Table 4. Clear cell RCC was the commonest variety followed by papillary RCC. Three patients had sarcomatoid RCC on the final histopathology. A total of 17 patients received adjuvant TKI therapy after wound healing, of which 12 had preoperatively diagnosed metastatic disease and five patients were deemed to be at high risk of progression based on adrenal involvement and perirenal fat involvement on histopathological examination. Local recurrence in renal fossa and ipsilateral psoas muscle was seen in four patients (7%) during follow-up, which were also treated with TKI therapy.

The overall survival (OS) at 2 and 5 years of nonmetastatic group was 81.1% and 47.5% respectively and in metastatic group was 35.1% and 0%, respectively. For nonmetastatic patients who received adjuvant TKI, OS at 2 and 5 years was 50% and 0%, respectively. The predictors of OS are enumerated in Table 5. Multivariate cox regression analysis showed significant differences in OS in patients having distant metastases (P = 0.014), margin positivity (P = 0.043), T-staging (P = 0.001) and tumour thrombus levels (P = 0.000) [Table 6].

DISCUSSION

The presence of tumor thrombus in the IVC in a case of RCC poses a technical challenge to the surgeon. Radical nephrectomy with the removal of the vena caval thrombus

Table 2: Intraoperative findings

Findings	Total, *n* (%)	Level of thrombus			
		I	II	III	IV
Numbers of patients (*n*)	56	23	20	7	6
Surgical approach					
Open	53 (94.6)	21	19	7	6
Laparoscopic	1 (1.8)	1	0	0	0
Laparoscopic-assisted open	2 (3.6)	1	1	0	0
Incision					
Chevron	17 (30.4)	4	10	3	0
Mercedes Benz	17 (30.4)	3	4	4	6
Subcostal	21 (37.5)	15	6	0	0
Need of bypass procedure	3 (5.4)	0	0	0	3
Sternotomy	7 (12.5)	0	0	2	5
Site of clamping					
Suprahepatic	13 (23.2)	0	3	7	3
Infrahepatic	40 (71.5)	23	17	0	0
Tumor invasion of IVC wall	11 (19.7)	2	5	2	2
Operating time (min) mean±SD	224±70	189±45	204±46	306±23	358±19
Blood loss (ml), mean±SD	749±450	447±134	760±372	971±125	1780±148
Lymphadenectomy	14 (25)	4	5	2	3
IVC patch repair	3 (5.4)	0	0	2	1
Liver mobilization	9 (16.1)	0	1	7	1

IVC=Inferior vena cava, SD=Standard deviation

Table 3: Postoperative outcomes

Outcomes	Total, *n* (%)	Level of thrombus			
		I	II	III	IV
Postoperative complications					
Nausea and vomiting	7 (12.5)	4	2	0	1
Atelectasis	5 (8.9)	0	3	1	1
Fever	6 (10.7)	2	2	2	0
IVC thrombosis	2 (3.6)	0	1	1	0
Paralytic ileus	3 (5.4)	3	0	0	0
Hypotension	3 (5.4)	0	1	0	2
Surgical site infection	1 (1.8)	1	0	0	0
Sepsis	1 (1.8)	0	1	0	0
Pulmonary embolism	1 (1.8)	0	0	0	1
Blood transfusion	11 (19.6)	0	4	3	4
Clavien Dindo grade					
Number of patients with Grade I as highest grade of complications	16 (29.6)	9	4	2	1
Number of patients with Grade II as highest grade of complications	15 (26.8)	1	5	5	4
Number of patients with Grade IIIa as highest grade of complications	1 (1.9)	0	1	0	0
Number of patients with Grade V complications	2 (3.7)	0	0	1	1
Length of hospital stay (mean±SD)	8.4±4.4	7.5±3.9	9.5±5	9±3.7	7.2±2.9

IVC=Inferior vena cava, SD=Standard deviation

is the treatment of choice in both nonmetastatic and metastatic settings, unless there are fitness factors precluding surgery.[7,10,11] In the metastatic setting, cytoreductive surgery along with targeted therapy improves OS.[12-15] It also avoids death due to pulmonary embolism that may result from inadvertent migration of the tumor thrombus from the IVC or right atrium into the pulmonary circulation. In our series, we also found improved OS (mean survival of 28.8 months) in12 patients with distant metastasis, who received TKI therapy (sunitinib or pazopanib) after surgery. In a series of 30 patients, cytoreductive nephrectomy and IVC thrombectomy in metastatic RCC achieved an actuarial survival rate of 17% and 80% of patients were able to complete immunotherapy.[16] Zisman *et al.* in their series of 207 patients of RCC with venous thrombi reported that these patients had similar OS rates irrespective of metastatic status and that cytoreductive nephrectomy with venous thrombus removal resulted in better response to immunotherapy.[17]

The use of neoadjuvant therapy with TKI is still investigational and understudy, especially in patients with IVC tumor thrombus. Shuch *et al.* stated that the use of neoadjuvant TKI may cause medical infarction of the thrombus due to their mechanism of action which involves inhibition of the VEGF pathway. So theoretically, the vascularity of the thrombus, which is often arterialized with its own independent blood supply, would decrease leading to a decrease in the size and

Table 4: Pathological findings and follow-up

Findings	Total, *n* (%)	Level I	Level II	Level III	Level IV
Tumor stage					
pT3b	36 (64.2)	21	13	2	0
pT3c	17 (30.4)	2	4	5	6
pT4	3 (5.4)	0	3	0	0
Fuhrman grade					
I	4 (7.1)	1	2	1	0
II	26 (46.4)	13	9	3	1
III	20 (35.7)	8	6	2	4
IV	6 (10.7)	1	3	1	1
Histopathology					
Clear cell carcinoma	43 (76.8)	19	14	6	4
Papillary carcinoma	9 (16.1)	3	3	1	2
Sarcomatoid differentiation	3 (5.4)	1	2	0	0
Rhabdoid differentiation	1 (1.8)	0	1	0	0
HPE LN status					
Positive	10 (17.8)	2	5	2	1
Surgical margins					
Number of patients with negative margins	42 (75)	18	15	5	4
Number of patients with perirenal fat involvement	11 (19.6)	6	4	1	0
Number of patients with ureteric margin involvement	1 (1.8)	0	0	1	0
Number of patients with contiguous adrenal involvement	2 (3.6)	0	1	1	0
Disease progression	28 (50)	7	11	6	4
Adjuvant therapy	17 (31.5)	8	6	3	0
Follow-up (months), mean±SD	44±27	54±26	42±30	26±8	23±3

HPE=Histopathological examination, LN=Lymph node, SD=Standard deviation

Table 5: Predictors of survival

Predictors	Mean survival (months)	95% CI	*P*
Total	50.2	42-58.5	
Distant metastases			
Present	26.8	19.8-33.7	0.000
Absent	56.5	47.3-65.7	
LN metastases			
Present	40.6	27.6-53.7	0.235
Absent	54.18	44.1-64	
Soft-tissue margin			
Positive	36.5	24.2-48.9	0.045
Negative	54	44.5-63.6	
Histopathology types			
Clear cell	57.31	47.6-67	0.003
Papillary	26.2	19.6-32.5	
Sarcomatoid differentiation	36.7	7.8-65.5	
Rhabdoid differentiation	34	34-34	
Tumour stage			
T3	52.3	44-60.7	0.000
T4	16.7	14-19.3	
Thrombus level			
I	63.5	52.3-74.7	0.000
II	50.1	35.3-64.8	
III	25.9	19.7-32	
IV	23.5	20.1-26.8	

CI=Confidence interval, LN=Lymph node

level of the thrombus, which in turn would facilitate easier removal or avoid a sternotomy, thus improving peri and post-operative outcomes. They found reduction in the level of thrombus from level II to level I after sunitinib therapy.[18] However many other authors found no such outcomes in their studies.[19,20] In our series we used neoadjuvant targeted therapy in six patients. One patient showed an improvement in performance status, making it possible for him to undergo surgery. The rest of the five patients showed a decrease in the level of thrombus along with decrease in diameter and vascularity and could successfully avoid bypass and even sternotomy in some of the cases. Hence, we believe that the use of neoadjuvant TKI does help in decreasing the size of the thrombus and facilitating less blood loss and ease of surgery, in addition to improving the preoperative performance status. However, these findings need to be validated in larger series. Preoperative angioembolization can be helpful when there is a large highly vascularized thrombus with independent supply from the renal artery or aorta, to shrink the thrombus to a more manageable level or to avoid bypass or liver mobilization. In our series five patients with large tumors (>12 cm with > level III thrombi) underwent angioembolization. However, except for decreased intraoperative bleeding during nephrectomy, no other effect on the level of the thrombus was noted. No patients who underwent angioembolisation received any neoadjuvant TKI therapy.

World over, there is an increasing body of literature on the use of minimally invasive techniques (robotic, laparoscopic) for radical nephrectomy and IVC thrombectomy. Some studies reported that laparoscopy can be an alternative to open surgery for level ≤ II thrombi and laparoscopic nephrectomy with open venotomy can be a safe option for level III/IV thrombi.[21,22] In our series, one patient underwent a total laparoscopic procedure for right-sided RCC with level II IVC thrombus, and another two patients underwent laparoscopic-assisted open technique for level II and level III thrombus. Robotic surgery services were unavailable in our institute during the study period. Bypass

Table 6: Cox regression analysis of overall survival

Variables	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*	Adjusted hazard ratio	95% CI	*P*
Age	1.013	0.975-1.051	0.514			
Tumour stage	0.066	0.015-0.295	0.000	0.045	0.008-0.262	0.001
LN metastases	0.661	0.327-1.335	0.248			
Distant metastases	0.259	0.114-0.590	0.001	0.266	0.093-0.763	0.014
Level of IVC thrombus						
I	0.130	0.036-0.465	0.002	0.040	0.008-0.195	0.000
II	0.192	0.054-0.689	0.011	0.057	0.012-0.262	0.000
III	0.750	0.213-2.64	0.654	0.155	0.028-0.873	0.035
Soft-tissue margin positivity	0.476	0.223-1.014	0.054	0.400	0.165-0.970	0.043
ECOG						
0	0.073	0.16-0.322	0.001			
1	0.135	0.032-0.568	0.006			
2	0.142	0.034-0.582	0.007			

CI=Confidence interval, IVC=Inferior vena cava, ECOG=Eastern Cooperative Oncology Group, LN=Lymph node

procedures, either cardiopulmonary or venovenous, are an integral part of any procedure for level III/IV procedures. However, for thrombus causing complete IVC obstruction with extensive collateralization, not extending into the right atrium or having IVC wall invasion, bypass procedure may not be needed. Sequential clamping of caudal IVC first, followed by contralateral renal vein, hepatic artery, portal vein, and lastly, cephalad IVC may be sufficient.[23] Liver mobilization may be necessary for suprahepatic IVC clamping. Even patients with non-obstructive IVC thrombus tolerate suprahepatic clamping quite well. Immediately after removal of the thrombus, suprahepatic clamp can be replaced with infrahepatic clamp, and Pringle maneuver can be released to further lower down liver ischemia times. In our series, only three patients underwent cardiopulmonary bypass for level IV thrombus extending into the right atrium which was successfully removed. In comparison to a previous study done from our institute a decade before,[11] which utilized venovenous bypass for most of the cases of level II/III thrombus, the present series managed to avoid it safely. The mean operating time found in our study was 214 min and average blood loss was 765 ml, which are comparable to the other similar series.[24] The OS improves after radical nephrectomy and IVC thrombectomy. Many studies reported a 5-year OS rate varying from 30% to 63%.[7,25,26] In our series, the 2-year and 5-year OS was 69.7% and 38.7% respectively. All the negative predictors of survival namely poor performance status, higher T stage, distant metastases and positive surgical margins found in our study correspond to those reported in other studies. Our study found the level of thrombus to be a significant predictor of survival. This is probably due to the smaller number of level III/IV thrombi. Literature also supports lymph nodes positivity, distant metastases, higher Fuhrman's grade, and variant histology as predictors of poor prognosis, which are reflected in our study.[27,28]

The limitations of our study are that it is a retrospective study with a small sample size. Hence, some of the findings such as, response to neoadjuvant TKI therapy and cytoreductive nephrectomy and IVC thrombectomy, need to be validated in larger series. However recent large trials like the CARMENA trial, did not mention any subset analysis on these groups of patients.[29,30] Maybe because, enrolling a large number of patients with RCC with IVC thrombus and metastases, fit enough to undergo cytoreductive nephrectomy followed by TKI therapy in a prospective study is a difficult task.

CONCLUSION

Almost 50% of patients with nonmetastatic RCC and IVC thrombus survive five years following surgery. Cytoreductive nephrectomy with IVC thrombectomy followed by TKI therapy in metastatic RCC with venous tumor thrombi also provides acceptable OS. The use of neoadjuvant TKI may help in decreasing the size of the thrombus facilitating easier surgical excision. Bypass procedures can be safely avoided for most level III thrombi with adequate preoperative planning.

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