

# Influence of tumor size in the progression of venous tumor thrombus in renal cell carcinoma: A 7-year single-center experience

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## Abstract

**Objective:** The objective of the study is to describe the perioperative outcomes, disease-specific, and overall survival status in patients diagnosed with renal cell carcinoma with inferior vena cava (IVC) tumor thrombus.

**Patients and Methods:** We did a retrospective analysis of all patients who underwent radical nephrectomy along with IVC thrombectomy from the year 2013 to 2020. Mayo's classification was used to stratify the level of IVC thrombus. Demographic, perioperative, histopathology data, complications, and survival status were analyzed.

**Results:** Total number of patients included in the study was 39, (Male: Female = 84.6%: 15.4%). Median age of patients was 58 (interquartile range [IQR] 50–63) years. Median size of renal tumor (in cms) was 9.5 (IQR 7.5–12), 8 (IQR 7–11.5), 8.5 (IQR 7–11.75), and 11 (IQR 9.5–11) ( $P = 0.998$ ) in level 1,2,3, and 4 tumors, respectively. Clear cell variant was seen in 32 patients (82%) with R0 resection in 17 patients. Twelve patients (30.7%) had systemic metastasis on presentation. The overall mean survival time was 66.4 months with 95% confidence interval (CI) (52.4–80.5 months). Mean recurrence-free survival is 76 months with (63–90) CI of 95%. Mean survival in patients who presented with metastasis is 47 months with 95% CI (52.4–80.5). Perioperative mortality rate was 5.12% in this study.

**Conclusion:** The tumor size does not have an influence on the progression of tumor thrombus into IVC. Significant difference in survival was observed between different levels of thrombus with high mortality in level four tumors.

**Keywords:** Inferior vena cava thrombectomy, nephrectomy, renal cell carcinoma

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## INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2%–3% of all malignancies, among which 3%–4% of RCC has tumor

thrombus extension into inferior vena cava (IVC) and 1% of tumor thrombus extends into the right atrium.<sup>[1]</sup> We present a 7 year, single-institution experience during which

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we have managed 39 cases of RCC with IVC thrombus with radical nephrectomy along with IVC thrombectomy.

## PATIENTS AND METHODS

This article is a retrospective observational study that was conducted in our hospital, where the data of all patients who underwent radical nephrectomy with inferior vena cava thrombectomy (RN-IVCT) between 2013 and 2020, were analysed ( $n = 39$ ).

### Methodology

All the patient's data who underwent RN-IVCT in the specified period were analyzed, after getting Institutional scientific and ethical committee clearance (awaited). Demographic data of patients, tumor laterality and dimensions, level of IVC thrombus, and comorbidities were analyzed. All the patients were operated under general anesthesia by a multidisciplinary surgical team inclusive of Urology, vascular surgery, and cardiothoracic surgery. The venous tumor thrombus (VTT) level was classified based on mayo classification for IVC tumor thrombus [Figure 1]. Postoperative parameters and complications were analyzed. Operative time, estimated blood loss, perioperative complications, mortality rate, cancer-specific, and overall survival status were evaluated. Complications were graded as per the modified Clavien-Dindo classification.<sup>[2]</sup> Histopathology reports were analyzed. Hospital medical records and phone call follow-ups were made to analyze the disease-free survival and overall survival status.

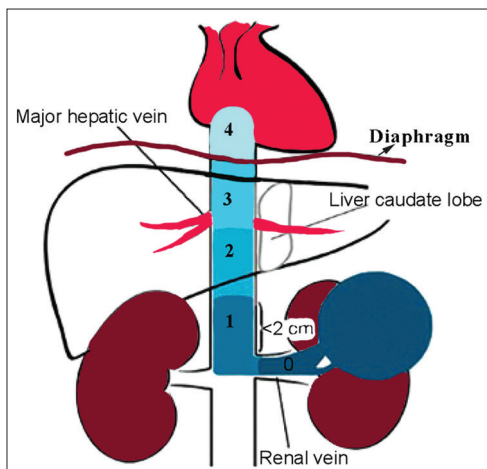
### Statistical analysis

All continuous variables were tested for normal distribution using Shapiro-Wilks' test. If they were normally distributed they were expressed as mean  $\pm$  standard deviation non normally distributed continuous variables were represented with median and interquartile range (IQR). Categorical

variables were represented by percentage and comparisons of the data were done by Chi-square test or Fisher's exact test. Comparison of normally distributed continuous variables between two groups was done by independent sample *t*-test and if the number of groups to be compared were more than three, we have used ANOVA. Nonnormally

**Table 1: Patient Characteristics**

PATIENT VARIABLES	NUMBER
Gender ( <i>n</i> )	
- Male	33 (84.6%)
- Female	6 (13.4%)
Median age and IQR ( years)	58(IQR 50-63) years
Laterality	
- Right	29 (74.3%)
- Left	10 (25.7%)
ECOG Status	
0	31 (79.4%)
1	8 (20.6%)
Level of tumor thrombus ( <i>n</i> )	
- Level I	06 (15.4%)
- Level II	17 (43.6%)
- Level III	12 (30.8%)
- Level IV	04 (10.2%)
Presenting symptoms ( <i>n</i> )	
Hematuria	20
Abdominal pain/loin pain	8
Weight loss	8
Pedal edema	6
Cough/breathlessness/hemoptysis	5
Mass abdomen	3
Low back ache	2
Weakness	2
Fever	2
Scrotal swelling	1
Distant metastases at presentation ( <i>n</i> )	12 (total) (30.7%)
Liver metastasis	2
Lung metastasis	8
Lung and liver metastasis	2
Cutaneous metastasis	1
Bone	1
Incision used:	
Mercedes Benz	5
Reverse -L	5
Sternotomy and Chevron	4
Chevron	10
Midline	9
Hockey Stick	6
Histological cell types	
- Clear cell	32 (82%)
- Sarcomatoid with clear cell	1 (2.5%)
- papillary	2 (5.1%)
- others	3 (7.7%)
Fuhrman grade (1, 2, 3, 4)	3,9,17,9
Positive Surgical Margins	$n=14$ (35.8%)
Kidney margins	0
Perinephric fat	3
Tumor thrombus	1
Renal vein and IVC	9
Renal vein and IVC + tumor thrombus	1
Renal vein and IVC + perinephric	2
Mortality rate	25.6%
Level 1 ( $n=6$ )	$n=2$ (33.3%)
Level 2 ( $n=17$ )	$n=3$ (17.6%)
Level 3 ( $n=12$ )	$n=3$ (25%)
Level 4 ( $n=4$ )	$n=2$ (50%)



**Figure 1: Mayo classification of inferior vena cava thrombus**

distributed continuous variables were compared by either Mann–Whitney U test or Kruskal–Wallis H test, based on the number of groups available. Overall survival estimated was computed by KaplanMeier method. Comparison of survival between the factors was made by Log-rank test. The statistical endpoint of our study was diseased specific and overall survival. All  $P < 0.05$  were considered statistically significant. Data entry was done in Microsoft Excel Windows 2007 and analysis was done with IBM Statistical Package for the Social Sciences (SPSS) (version 25.0), Statistics for windows, Armonk; NY, USA: IBM Corp.

## RESULTS

The total number of patients included in our study was 39, out of which 33 (84.6%) were males. The demographic data of the patients were discussed in Table 1. Median age of patients was 58 (IQR 50–63) years. Median size of renal tumor (in cms) was 9.5 (IQR 8–12), 8 (IQR 7–11), 8.5 (IQR 7–11.5), and 11 (IQR 10–11) ( $P = 0.583$ ) in level 1,2,3, and 4 tumors, respectively, and the median operating time was 3 (IQR 3–3 h), 4 (IQR 3–4.75 h), 5 (IQR 4.5–5 h), and 8.75 (IQR 8–12.12 h), ( $P = 0.001$ ) for level 1,2,3, and 4 tumors, respectively. Eastern cooperative oncology group (ECOG) performance status was 0 for 31 patients and one for eight patients. Hematuria was the most common presenting symptom, followed by abdominal pain and weight loss. Twelve patients (30.7%) presented with distant metastasis on initial presentation [Table 1]. Median blood loss was level 450 (IQR 237–500 ml), 600 (IQR 300–1200 ml), 1100

(IQR 550–3250 ml), and 1900 (IQR 1500–2750 ml) for level 1,2,3, and 4 tumors, respectively. There was a significant difference in the proportion of blood loss between the different levels, ( $P = 0.006$ ). Histopathology revealed that the most common variant is clear cell cancer, seen in 32 patients (82.05%). The complications are displayed in Table 2. The overall mean survival time was 66.4 months with 95% confidence interval (CI) (52.4–80.5 months). Mean recurrence-free survival is 76 months with (63–90) CI of 95%. The mean overall survival in patients with metastasis was 47 months with 95% CI (26.9–68 months) and in patients with no initial metastasis was 66.4 months with 95%CI (52.4–80.5 months), which was not statistically significant ( $P = 0.526$ ). Perioperative mortality rate was 5.12% in this study. Mortality rate within each levels were 33.3%, 11.8%, 25%, and 50% for level 1,2,3, and 4 tumors, respectively. Paradoxical higher mortality in level 1 is because of less number of cases ( $n = 6$ ) and two deaths which happened in elderly gentlemen with high-grade disease, distant metastasis, and margin positivity. The hospital stay was more in level 3 and 4 patients but was not statistically significant ( $P = 0.112$ ). The overall mortality rate was 25.64% in our series. Seven patients were lost to follow-up in our series (17.9%).

## DISCUSSION

About 3% of all cancers are constituted by RCC with the ability of vascular invasion, mainly along the renal vein and IVC up to the right atrium. Hevia, *et al.* in their study stated that VTT formation is seen in approximately 4%–10% of RCC patients, and complete surgical removal is the only curative option in cases without distance metastasis.<sup>[3-6]</sup> In our institute, over the past 8 years, 671 radical nephrectomies were done for RCC among which 39 patients had VTT, and underwent RN-IVCT during the time period, which is 5.8% of the total radical nephrectomy cases. Patients rarely present with a classical triad of pain, hematuria, or a palpable mass, most being asymptomatic. Some patients may develop paraneoplastic syndrome or present with distant metastases at initial presentation.<sup>[7]</sup> Presenting symptoms in our study is given in Table 1. Complete blood and renal evaluation followed by preoperative magnetic resonance imaging (MRI) or contrast-enhanced computerized tomography (CECT) are required to assess the tumor characteristics, level, and dimensions of the VTT. MRI is the Gold Standard (sensitivity 96%–100%) for assessing the level of tumor thrombi in the IVC and for RCC staging. But with availability of high quality multidetector CECT, the need for MRI is getting reduced in patients with normal renal functions. Only one patient underwent MRI, due to renal insufficiency in our study. All

**Table 2: Complications**

INTRA-OPERATIVE COMPLICATIONS	NUMBER OF CASES
Pulmonary embolism	0
Cardiopulmonary arrest	2
Massive transfusion	5
POST-OPERATIVE COMPLICATIONS	NUMBER OF CASES
Cardiovascular	
- MI, CCF - IABP + coronary stenting	0
-Cardiogenic shock	1
- Requiring Inotropes	2
Respiratory	
- Atelectasis	12
- respiratory failure and prolonged ventilation	1
- Pulmonary embolism	0
Renal	
- AKI	11
-Electrolyte imbalance (Hyponatremia)	01
Sepsis	01
Gastro-intestinal	
- Gastric ileus	20
Others (DIC)	1
CLAVEIN DINDO COMPLICATIONS	
-Grade 1/II	28
-Grade III	0
-Grade IV	3
-Grade V	2

other patients underwent CECT or came with CECT done in outside hospitals. The mayo classification is widely used to stage VTT [Figure 1].<sup>[8]</sup> Since stage III may involve the intrahepatic or supra-hepatic and infra-diaphragmatic IVC and stage IV involves the right atrium, Transesophageal echocardiography is used for a correct staging of the level III or IV thrombi and also plays an important role intraoperatively.<sup>[3,4,7]</sup> An aggressive attitude is needed when the IVC is involved.<sup>[7,9]</sup>

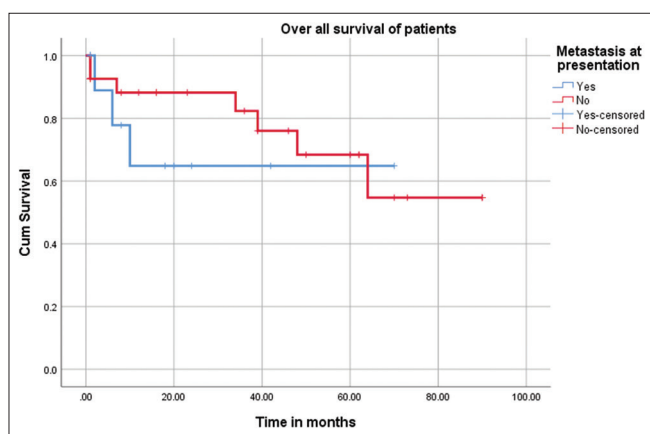
RN-IVCT is a complex procedure that warrants experienced multidisciplinary team input involving urological, cardiothoracic, vascular, and sometimes hepatobiliary surgeons. Renal vasculature control, hepatic mobilization, suprahepatic IVC clamping, and Pringle maneuvers may be needed based on VTT level.<sup>[9]</sup> There can be a significant risk to the patient, with perioperative mortality being 5%–8%.<sup>[10]</sup> Although some surgeons have advised cardiopulmonary bypass (CPB) (with/without deep hypothermic circulatory arrest) for removal of level III and IV thrombi, Wang *et al.*, advocated that this is not required always.<sup>[9]</sup> However, CPB with hypothermia and low antegrade flow was used for three patients of level IV thrombi in our experience. This facilitated “milking” the thrombus without compromising organ perfusion. While studies have reported pulmonary emboli this was not observed in their study.<sup>[7,9]</sup>

Prognosis depends on various factors such as symptoms at presentation, metastasis, and Level of VTT.<sup>[11]</sup> Cho, *et al.* in their study stated that important prognostic factors were body mass index (BMI), advanced disease at presentation, IVC, and lymph node infiltration, and Fuhrman grade. VTT level did not affect the prognosis.<sup>[12]</sup> Surgical resection alone gives a 46%–51%, 5 year CSS.<sup>[13,14]</sup> In our study, we had 12 cases (30.7%) with distant metastasis [Table 1]. Among them, two patients with hepatic involvement and one patient with a chest wall nodule underwent metastasectomy

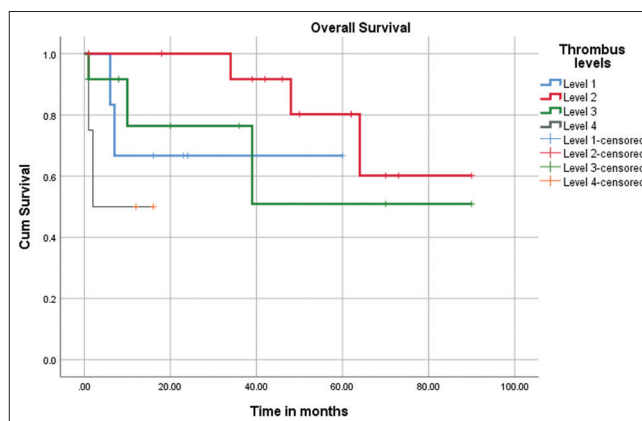
along with RN-IVCT.<sup>[7,9,10]</sup> These patients were offered metastasectomy because of their relatively young age and better ECOG status since an R-0 resection in them can improve their quality of life. Among the 13 patients who presented with initial metastasis, six patients received sunitinib or pazopanib, one patient was offered radiotherapy and targeted therapy, one patient survived only for 2 months and other five patients were lost to follow-up. The mean overall survival in patients with metastasis who had cytoreductive surgery and postoperative chemotherapy was 47 months with 95% CI (26.9–68 months) and in patients with no initial metastasis was 66.4 months with 95%CI (52.4–80.5 months). Even though there was a 20 months survival difference, this was not found to be statistically significant ( $P = 0.526$ ) [Figure 2].

The mean age of patients in our review was  $55.2 \pm 8.8$  years which was similar to Kishore, *et al.*, ( $56.5 \pm 12.3$ ) and Cho *et al.* ( $55.5 \pm 11.6$ ) and less than Kulkarni *et al.* and Wang *et al.* studies. The mean BMI in our series was  $25.08 \pm 3.23$  kg/m<sup>2</sup> and in patients who died in the immediate postoperative period, it was  $19 \pm 1.3$  kg/m<sup>2</sup>. This could be attributed to cancer cachexia and could be a confounding factor. Many works of the literature indicated that BMI is a distinct risk factor for prognosis in IVC resection during thrombectomy.<sup>[4,9,12]</sup> People with high BMI are at an increased risk of developing RCC (relative risk of 1.07 times). But in already developed RCC, higher BMI has a good prognosis. This paradox may be due to adipose tissue’s endocrine function and the requirement of more energy to battle cancer.<sup>[4]</sup> Cho *et al.* suggested that in the multivariate model, low BMI was an independent prognostic factor for Recurrence-free survival and was associated with cachexia.<sup>[12]</sup>

Median size of renal tumor (in cms) was 9.5 (IQR 8–12), 8 (IQR 7–11), 8.5 (IQR 7–11.5), and 11



**Figure 2:** Kaplan-Meier survival graph in metastatic and nonmetastatic patients



**Figure 3:** TT level-specific Kaplan-Meier survival graph

**Table 3: Literature Review**

LITERATURE	COMPLICATION RATE (%)	OVERALL SURVIVAL (months)	FOLLOW UP (months)	PERI-OPERATIVE MORTALITY (%)	MALE: FEMALE RATIO	RIGHT :LEFT	ESTIMATED BLOOD LOSS (EBL) ml/UNITS TRANSFUSED
Our study (n=36)	70.1%	Overall mean survival time was 66.4 months with 95%CI (52.4-80.5 months)	Median follow-up: 20months (IQR 2-50)	Overall mortality rate in our study was 25.6%. Peri-operative mortality is 5.12%	5:1	3:1	EBL- 1290 ml (IQR- 400-1575 ml). Units transfused-3.86: IQR- (2-6)
Kaag MG <i>et al.</i> (n=78)	18%	Median overall survival was 55.5 months	Median follow-up: 51 months	Mortality rate of 6%.	3.3:1		EBL - 1300 mL (IQR 750–2500). Median units transfused-3(IQR 2–7)
Wang GJ <i>et al.</i> (n=23)	8.69%		Median follow up: 15 months.	Mortality rate of 8.7%.	3.6:1		EBL- 2800ml.
Kulkarni J <i>et al.</i> (n=100)	38%	Overall 5 year survival- 63%.		Immediate post-operative mortality was 2%	2:1	2:1	The mean blood transfusion - 3.1 units, 3.8 units & 5.6 units (Midline abdomen, Additional sternotomy only, Additional CPB & deep hypothermia)
Casey, R. G., <i>et al.</i> (n=22)	45.5%	Median overall survival 29 months	Median follow up: 46.3 months	Mortality rate of 9%.	3:1	2.4:1	Transfusion varied between laparotomy only, sternotomy, and CPB (2 (range 0-11) vs. 6.5 (range 2-21) vs. 4 (range 1-12)).
Kishore, Thekke Adiyat, <i>et al.</i> (n=13)	30.7%	Overall survival 100%	The mean follow-up -19 months	Nil		5.5:1	EBL-395 mL (SD+/-170).
Cho, Min Chul, <i>et al.</i> (n=124)		Median survival period was 50 months.	Median follow-up- 29.0 months.	Mortality rate of 52.4%	2.1:1	1:2.6	

(IQR 10–11) ( $P = 0.583$ ) in level 1,2,3, and 4 tumors, respectively. In Kaag *et al.*, the median tumor diameter was 9.5 cms (IQR 8–12.2) and in Casey, *et al.*, the median tumor size was 9.9 cm (IQR 4–20).<sup>[5,10]</sup> The median operating time was 3 (IQR 3–3 h), 4 (IQR 3–4.75 h), 5 (IQR 4.5–5 h), and 8.75 (IQR 8–12.12 h), ( $P = 0.001$ ) for level 1,2,3, and 4 tumors, respectively. Evidently, Level 4 tumors required more time for resection. This was similar to other studies where higher-grade tumors required more time.<sup>[10,15]</sup> In Casey, *et al.* and Kulkarni *et al.*, mean operative time were 3.75 and 4.1 h, respectively. Additional time was needed for sternotomy and CPB groups.<sup>[5,7]</sup>

In a study by Kishore *et al.*, all patients had negative margins whereas in Kaag *et al.* positive surgical margin was seen in 8% of cases.<sup>[10,15]</sup> In our study 13 (36.1%) patients had positive margins among which nine patients had renal vein and IVC margin positivity in the Hewlett Packard Enterprise report. This high margin positivity and residual disease in our study could be partly owed to the fact that 33 patients (84.6%) of patients having levels 2,3, and 4 VTT. The transfusion rate was 77.7% in our study ( $n = 28$ ). Five patients required massive transfusion.

The minor complication rate (Clavien-Dindo 1 and 2) was 70.1% in our study and 7.69% for Clavien-Dindo level 4 and 5.12% for Clavien-Dindo level 5 complications [Table 2]. Overall complications rate was high up to 70% in a few

studies.<sup>[16]</sup> Clear cell carcinoma was the most common variant of tumors in our study which was similar to the studies by Kulkarni *et al.*, Kishore, *et al.* and Wang, *et al.* The overall mean survival time was 66.4 months with 95% CI (52.4–80.5 months). Kaplan-Meier survival analysis [Figure 3] and the Log-rank test showed no significant difference in their overall survival, ( $P = 0.095$ ) between different levels of thrombus.

The mean hospital stay in our study was  $7.09 \pm 3.31$  days and was more in level 3 and 4 patients, however, it was not statistically significant ( $P = 0.112$ ). Other contemporary studies showed similar results. The median hospital stay in Kaag *et al.* was 7 (IQR-5–11) days.<sup>[10]</sup> The mean hospital stay for Kishore, *et al.* was 7.8 days (SD-3.27) and for Kulkarni *et al.* it was 8.2 and 12.2 days, respectively, for midline abdominal approach and CPB.<sup>[7,15]</sup> The overall mortality rate in our study was 25.6% while mortality rate among different levels of VTT is mentioned in Table 1, ( $P = 0.094$ ). The overall mortality ranges from 2.7% to 13% [Table 3] in contemporary studies.<sup>[17]</sup> Overall 5-year survival rate in our series is 65.5%. While overall 5-year survival in patients with metastasis was 64.8% and in patients with no metastasis, it was 68.4%.

The present study is a retrospective evaluation of a single-institution experience and is subjected to biases and limitations. The less number of patients in the study

can limit the conclusion that could be extrapolated to the other wider scientific studies and the general population. The disease-free survival status could not be precisely found due to the loss of follow-up of patients (17%) and limitations in the available hospital records.

In summary, overall survival in our study was similar to other contemporary studies. The level of VTT was not related to the tumor size and the tumor size was not a deciding factor in the progression of tumor thrombus into IVC. There was no statistically significant difference in survival between different levels of thrombus. Mortality was high in level 4 tumors. Surgical modality should be the foremost mode of treatment even in patients with high disease load and metastasis.

Despite the fairly small cohort in our retrospective, observational study, it has demonstrated that through cautious patient selection and availability of an experienced multidisciplinary surgical team along with a well-equipped critical care unit, RN-IVCT can be done to decrease morbidity and mortality. Aggressive surgical resection along with adjuvant chemotherapy and/or immunotherapy can give an acceptable quality of life postsurgery, and we suggest, more robust, prospective studies to carry forward the findings of the study.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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