

# Radical Nephrectomy in Renal Cell Carcinoma with Venous Tumoral Thrombus: Long-term Outcomes and Overall Survival

## *Nefrectomía radical en carcinoma de células renales con trombo tumoral venoso: Desenlaces a largo plazo y supervivencia global*

Aysa Vanessa Mosquera<sup>1</sup>  Catalina Barco-Castillo<sup>1</sup>  Diego Camacho<sup>2,3</sup> José Correa<sup>4</sup>  
Rodolfo Varela<sup>2,3,5</sup> Danilo Citarella<sup>1,6</sup> Marino Cabrera<sup>2,3,6</sup>

<sup>1</sup>Department of Urology, Hospital Militar Central, Bogotá DC, Colombia and Universidad Militar Nueva Granada School of Medicine, Urology Residency Program, Bogotá DC, Colombia

<sup>2</sup>Universidad Nacional School of Medicine, Bogotá DC, Colombia

<sup>3</sup>Department of Urology, Fundación Clínica Shaio, Bogotá DC, Colombia

<sup>4</sup>Universidad del Rosario School of Medicine, Bogotá DC, Colombia

<sup>5</sup>Facultad de Medicina, Universidad Nacional de Colombia, Bogotá DC, Colombia

<sup>6</sup>Department of Urology, Fundación Clínica Shaio, Bogotá DC, Colombia

Address for correspondence Aysa Vanessa Mosquera, urologist, Departamento de Urología, Hospital Militar Central, TV 3 49 00, Bogotá DC, Bogotá, Colombia  
(e-mail: vanessa.mosquera1991@gmail.com).

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### Abstract

**Objective** To describe the five-year overall survival (OS) and perioperative morbidity of patients with renal cell carcinoma (RCC) with venous tumor thrombus (VTT) treated through radical nephrectomy and thrombectomy.

**Materials and Methods** We evaluated a cohort of 530 patients with a diagnosis of RCC from January 2009 to December 2019, and found VTT in 42 of them; these 42 patients composed the study sample. The patients were stratified according to the Neves Thrombus Classification (NTC). The baseline and perioperative characteristics, as well as the follow-up, were described. The Kaplan-Meier curve and its respective Cox regression were applied to present the 5-year OS and the OS stratified by the NTC.

**Results** The average age of the sample was of  $63.19 \pm 10.7$  years, and there were no differences regarding gender. In total, VTT was present in 7.9% of the patients. According to the NTC, 30.9% of the cases corresponded to level I, 21.4%, to level II, 26.1%, to level III, and 21.4%, to level IV. The 5-year OS was of 88%. For level-I and level-II patients, the 5-year OS was of 100%, and of only 38% among level-IV patients. Complications, mostly minor, occurred in 57% of the cases.

### Keywords

- renal cell carcinoma
- venous tumor thrombus
- Neves thrombus classification
- survival analysis

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## Resumen

### Palabras clave

- carcinoma de células renales
- trombo tumoral venoso
- clasificación de trombos de Neves
- análisis de supervivencia

**Conclusiones** Radical nephrectomy with thrombectomy is a morbid procedure; however, most complications are minor, and the five-year mortality is null for patients in NTC levels I and II, and low for levels III and IV, and it may be even lower in level-III patients when standardizing transesophageal echocardiogram intraoperatively and routine extracorporeal bypass. Thus, we recommend considering this surgery as the first-line management in patients with RCC and VTT.

**Objetivo** Describir la supervivencia global (SG) a los cinco años y la morbilidad perioperatoria de pacientes con carcinoma de células renales (CCR) con trombo tumoral venoso (TTV) tratados por nefrectomía radical y trombectomía.

**Materiales y Métodos** Se evaluó una cohorte de 530 pacientes con diagnóstico de CCR entre enero de 2009 y diciembre de 2019, y se encontró TTV en 42 de ellos; esos 42 pacientes compusieron la muestra de este estudio. Los pacientes fueron estratificados según la clasificación de trombos de Neves (CTN). Se describieron las características basales y perioperatorias de los pacientes, así como el seguimiento. Se aplicaron la curva de Kaplan-Meier y su respectiva regresión de COX para presentar la SG a los 5 años y la SG estratificada por CTN.

**Resultados** La edad promedio de la muestra fue de  $63,19 \pm 10,7$  años, sin diferencia respecto a género. El TTV estuvo presente en el 7,9% de los pacientes. Según la CTN, el 30,9% de los casos correspondía al nivel I, el 21,4%, al nivel II, el 26,1%, al nivel III, y el 21,4%, al nivel IV. La SG a los 5 años fue del 88%. Para los niveles I y II, la SG a los 5 años fue del 100%, y, para el nivel IV del 38%. Las complicaciones, menores en su mayoría, ocurrieron en el 57% de los casos.

**Conclusiones** La nefrectomía radical con trombectomía es un procedimiento morbido; sin embargo, la mayoría de las complicaciones son menores, y la mortalidad a los 5 años es nula cuando en los pacientes de niveles I y II en la CTN, y baja en los niveles III y IV, y puede ser incluso menor en los pacientes de nivel III al estandarizar el ecocardiograma transesofágico intraoperatorio y el baipás extracorpóreo rutinario. Por ello, recomendamos considerar esta cirugía como manejo de primera línea en pacientes con CCR y TTV.

## Introduction

Renal cancer corresponds to 2% to 3% of the cases of cancer worldwide, and it causes 1.7% of all deaths attributed to cancer.<sup>1</sup> Renal cell carcinoma (RCC) is the main type of renal cancer and the second most common urological malignancy in the world, with an annual incidence of 1.8%.<sup>1</sup> When diagnosed, up to 30% of patients will present locally-advanced disease, and 10%, venous tumor thrombus (VTT),<sup>2,3</sup> which occurs due to tropism of the RCC for vascular tissue in the inferior vena cava (IVC).<sup>3</sup>

The Neves thrombus classification (NTC), also known as Neves-Zincke VTT classification, was presented for the first time in 1987, and it describes the compromise of the VTT. Level I represents thrombus at the renal vein, level II, at the infrahepatic IVC, level III, at the retrohepatic IVC, and Level IV, at the subdiaphragmatic IVC or right atrium.<sup>4</sup>

The 5-year overall survival (OS) of patients with RCC and VTT reaches 40% to 68% with surgical management.<sup>4,5</sup> Thus, complete excision of these tumors and thrombectomy is now considered the first-line treatment with curative in-

attention. However, this approach is associated with high morbidity and mortality, and represents a challenge to surgeons (urologist and vascular) and anesthesiologists in cases of higher NTC levels, representing the need of intraoperative transesophageal echocardiogram and extracorporeal bypass.

The objective of the present study was to describe the 5-year OS and the perioperative characteristics and morbidity of patients with RCC and VTT treated through radical nephrectomy (RN) and thrombectomy.

## Methods

### Patient Selection

A retrospective cohort of 530 patients from four oncological centers with RCC who underwent RN was evaluated from January 2009 to December 2019. Each institutional Ethics Committee approved the protocol under the Declaration of Helsinki (IRB 2020037). From these patients, 42 presented with VTT and became the sample of the present study. They were followed up for up to 60 months (or less, in case of death).

The perioperative characteristics and follow-up history were evaluated from the clinical records of each patient and registered in a standardized database using Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, United States) spreadsheets. The tumor, node, metastasis (TNM) system<sup>2</sup> was used for staging, and the determination of the VTT level on the NTC<sup>4</sup> was based on magnetic resonance imaging (MRI) scans. All patients were submitted to RN and thrombectomy.

### Surgical Technique

The surgical approach was performed through a median laparotomy or anterior subcostal incision, and cardiovascular or vascular surgeons assisted the procedure for level-III and -IV patients. Cases of level-I thrombus were usually isolated with a vascular clamp and the approach was performed comfortably through the renal ostium, closing the IVC defect.

The procedure for level-II patients began with sequential clamping of the caudal IVC, contralateral renal vein, and cephalic IVC, with a posterior incision of the renal ostium and removal of the thrombus. After vascular control, a cavotomy from the renal ostium toward the head to the thrombus was performed, followed by cavorrhaphy removal of the IVC clamp, the contralateral renal clamp, and the proximal clamp.

Vascular control for level-III and -IV patients required a larger dissection, cardiopulmonary bypass, use of transesophageal echocardiography, hepatic mobilization to expose the retrohepatic IVC, and maneuvers that enabled the temporary occlusion of the portal triad, such as the Pringle maneuver. Division of the coronary and triangular ligament can be performed to enable rotation of the right hepatic lobe. The aforementioned cavotomy and cavorrhaphy procedures were performed. In case of involvement of the venous wall, the segment was resected, and vascular reconstruction was performed with synthetic or biological grafts.<sup>2</sup>

### Postoperative Outcomes

In the postoperative period, the complications were described through the Clavien-Dindo Classification,<sup>2</sup> and divided as minor (I-II) and major (III-IV) complications, and death (V). For the data analysis, stratification of the groups was performed according to their NTC level.

### Statistical Analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for MacOS, IBM Corp., Armonk, NY, United States) software, version 25.0. All qualitative variables were reported as frequencies and analyzed through the Chi-squared test. The quantitative variables were analyzed through the Shapiro-Wilk normality test and reported as mean  $\pm$  standard deviation if parametric, and as medians median and interquartile ranges (IQRs) if non-parametric. The comparison of means was performed through analysis of variance (ANOVA), and the median differences were compared through the Kruskal-Wallis test. Survival was evaluated through Kaplan-Meier curves, and the differences among the groups were analyzed through Cox regression. Values of  $p < 0.05$  were considered statistically significant.

## Results

The sample was composed of 42 (7.9%) patients with RCC and VTT. The average age was of  $63.19 \pm 10.7$  years. As for gender, 47.6% were female and 52.4%, male. In total, 85.7% of the patients had some symptoms at the moment of the diagnosis, most commonly hematuria (35.7%). Up to 60% of the cases were grade 1 on the Eastern Cooperative Oncology Group (ECOG) performance status score. As for the TNM stage, 92.9% of the patients were cT3, 26%, cN1, and 28%, M1. A total of 30.9% of the cases were of level I on the NTC; 21.4% were level II; 26.1%, level II; and 21.4%, level IV. All baseline characteristics of the patients are shown in **►Table 1**.

The median surgical time was of 282.5 minutes (IQR: 184–435), and it was longer for level-IV patients in comparison with those in other levels ( $p < 0.001$ ). Extracorporeal bypass was required in 9 patients, 88.9% of whom were level IV, and 9.1%, level III on the NTC ( $p < 0.001$ ). Intraoperative transesophageal echocardiogram was used in 100% of level-IV patients and in 36% of those in level III. Only one patient required IVC reconstruction with pericardial patch.

Overall, 57% of the patients presented complications. In terms of the NTC, complications occurred in 38% of level-I patients, in 22% of level-II, in 81% of level-II, and in 88% of level-IV patients. Most complications were minor, and major complications only occurred in 19% of patients and were related to those in higher NTC levels. When stratified by N, there were no significant differences in terms of complications among the groups (level I,  $p = 0.640$ ; level III,  $p = 0.110$ ; level IV,  $p = 0.306$ ).

Transfusion was needed in 69% of the cases (level I: 38%; level II: 77.8%; level III: 81.8%; and level IV: 88.9%;  $p = 0.037$ ). The median length of stay was of 6 days (IQR: 3–10 days), and it was longer among level-IV patients ( $p = 0.081$ ). All perioperative characteristics are shown in **►Table 2**.

The 5-year OS was of 88.1% (**►Fig. 1**). When stratified by NTC levels, it was of 100% among level-I and -II patients, of 72% among level-III patients with a hazard ratio (HR) of 11.5 (95% confidence interval [95%CI]: 4.43–12.3;  $p = 0.006$ ), and of 38% among level-IV patients, with an HR of 11.94 (95%CI: 9.74–12.3;  $p = 0.007$ ) (**►Fig. 2**).

## Discussion

Commonly, 10% of RCC with VTT had been reported.<sup>3</sup> In the series of the present study, the prevalence of venous invasion was of 7.9%. If left untreated, the prognosis for these patients is poor. They achieve a mean overall survival of 5 months and a cancer-specific survival (CSS) of only 29% at 1 year compared with patients submitted to surgical management, who can reach a rate of up to 65% at 5 years.<sup>6</sup> The total risk of complications in thrombectomy ranges from 50% to 78%, and bleeding requiring transfusion is the most common.<sup>7</sup> However, with the advances in perioperative care, imaging, expertise in cardio or vascular anesthesia, and surgery, the surgical management is not only feasible, it can be considered the first line of treatment in these patients.

**Table 1** Baseline characteristics of the sample

	Global(n=42)	NTC level I (n=13)	NTC level II (n=9)	NTC level III (n=11)	NTC level IV (n=9)	p-value
Age (years) – mean ± standard deviation	63.19 ± 10.7	60.54 ± 11.61	68.33 ± 11.61	62.73 ± 9.97	62.44 ± 9.1	0.412
<b>Gender – n (%)</b>						
Female	20 (47.6)	4 (30.8)	6 (66.7)	4 (36.4)	6 (66.7)	0.199
Male	22 (52.4)	9 (69.1)	3 (33.3)	7 (63.6)	3 (33.3)	
<b>Clinical presentation – n (%)</b>						
PTE	4 (9.5)	0 (0)	0 (0)	3 (27.3)	1 (11.1)	0.140
Hematuria	15 (35.7)	5 (38.5)	4 (44.4)	1 (9.1)	5 (55.6)	
Abdominal pain	13 (31)	3 (23.1)	3 (33.3)	5 (45.4)	2 (22.2)	
Abdominal mass	1 (2.4)	1 (7.7)	0 (0)	0 (0)	0 (0)	
UTI	3 (7.1)	1 (7.7)	2 (22.2)	0 (0)	0 (0)	
<b>Incidental finding</b>	<b>1 (2.4)</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>0 (0)</b>	<b>1 (11.1)</b>	
<b>Tumor, node, metastasis (TNM) staging – n (%)</b>						
<b>T</b>						
3	39 (92.9)	12 (92.3)	9 (100)	11 (100)	7 (77.8)	0.201
4	3 (7.1)	1 (7.7)	0 (0)	0 (0)	2 (22.2)	
<b>N</b>						
0	31 (73.8)	9 (69.1)	9 (100)	7 (63.6)	6 (66.7)	0.245
1	11 (26.2)	4 (30.8)	0 (0)	4 (36.4)	3 (33.3)	
<b>M</b>						
0	30 (71.4)	9 (69.1)	8 (88.9)	6 (54.5)	7 (77.8)	0.378
1	12 (28.6)	4 (30.8)	1 (11.1)	5 (45.4)	2 (22.2)	
<b>Eastern Cooperative Oncology Group (ECOG) performance status score – n (%)</b>						
0	16 (38.1)	5 (38.5)	6 (66.7)	3 (27.3)	2 (22.2)	0.240
1	25 (59.5)	8 (61.5)	3 (33.3)	8 (72.7)	6 (66.7)	
2	1 (2.4)	0 (0)	0 (0)	0 (0)	1 (11.1)	

Abbreviations: NTC, Neves Thrombus Classification; PTE, pulmonary thromboembolism; UTI, urinary tract infection.

Regarding the prognosis, we found an 5-year OS rate of 88.1%, and mortality among level-III and -IV patients was 11 times higher when compared with that of level-I patients. These results could be explained by the promotion of bypass availability in level-III patients, the use of intraoperative transesophageal echocardiogram for those in levels III and IV, the good perioperative performance status of our cohort, and the expertise of the oncologic centers.

Our results showed a higher risk of mortality among patients in levels III (HR: 11.5) and IV (HR: 11.94). The NTC level is a debated prognostic factor. In a study conducted at the University of Miami,<sup>8</sup> on the multivariate analysis, the authors only found as independent prognostic factors higher nuclear grade, metastasis at presentation, and non-clear-cell histology, but not the NTC level. Moreover, Wagner et al.<sup>9</sup> found that the NTC level was not related to worse outcomes. However, our results suggest a correlation between survival and the NTC level.

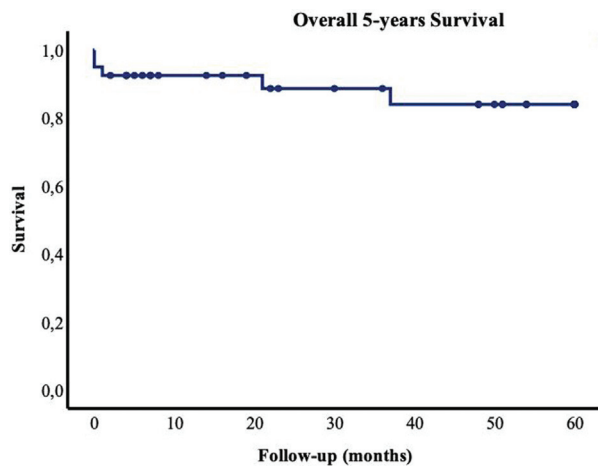
In our series, an overall complication rate of 57% was reported, with a rate of 19% of major complications and a rate of perioperative mortality of 7.1%. Our results show a higher rate when compared with the one found by Zhang et al.,<sup>10</sup> who reported rates of 12.5% of major complications and of 2.5% of perioperative mortality. However, it should be clarified that up to 20% of our population was composed of level-IV patients, which may explain our results. In a study<sup>11</sup> among level-III and IV patients, the rate of perioperative mortality was of 11%. In a study conducted at the Mayo Clinic,<sup>12</sup> the authors found that the rate of complications was higher in relation to the NTC level: level I:8.6%; level II: 15.2%; level III: 14.1%; and level IV: 17.9%, which is in line with the findings of the present study.

Several studies have been performed on the prediction of complications, and the most recent one,<sup>10</sup> published in 2019, proposes a nomogram with a c index of 0.794, with the most important independent factor being NTC levels III and IV, and their relationship with respiratory, hepatic and transfusion

**Table 2** Perioperative characteristics of the patients

	Global(n = 42)	NTC level I(n = 13)	NTC level II(n = 9)	NTC level III(n = 11)	NTC level IV(n = 9)	p-value
Surgical time (minutes): median [IQR]	282.5 [180-435]	180 [169.5-230]	240 [180-370]	350 [250-480]	459 [425-570]	0.000
Extracorporeal bypass – n (%)	9 (21.4)	0 (0)	0 (0)	1 (9.1)	8 (88.9)	0.000
Transesophageal echocardiogram – n (%)	13 (31)	0 (0)	0 (0)	3 (36.4)	9 (100)	0.000
IVC clamping – n (%)	25 (61)	1 (7.7)	6 (66.7)	11 (100)	9 (100)	0.000
Pericardial patch – n (%)	1 (2.4)	0 (0)	0 (0)	1 (9.1)	0 (0)	0.424
Clavien-Dindo complications – n (%)	23 (54.7)	5 (38.4)	2 (22.2)	9 (81.8)	7 (77.7)	0.361
I-II	12 (28.5)	3 (23)	2 (22.2)	5 (45.4)	2 (22.2)	
III-IV	8 (19)	2 (15.4)	0 (0)	3 (27.3)	3 (33.3)	
V	3 (7.14)	0 (0)	0 (0)	1 (9.1)	2 (22.2)	
Bleeding (mL): median [IQR]	1300 [750-3500]	500 [300-1500]	1000 [800-2500]	4500 [1500-5000]	2000 [1110-4400]	0.008
Need of transfusion – n (%)	29 (69)	5 (38.5)	7 (77.8)	9 (81.8)	8 (88.9)	0.037
Number of units transfused: median [IQR]	2 [0-5.25]	0 [0-2]	3 [1-4.5]	5 [0-7]	6 [0-8]	0.079
Hospitalization time (days): median [IQR]	6 [3-10]	3 [1-6]	6 [4-9]	7 [4-10]	9 [3-30.5]	0.081
<b>Thrombus pathology – n (%)</b>						
Clear cells	38 (90.5)	13 (100)	8 (88.9)	9 (81.8)	8 (88.9)	0.442
Papillary	2 (4.8)	0 (0)	1 (11.1)	1 (9.1)	0 (0)	
Chromophobe	1 (2.4)	0 (0)	0 (0)	0 (0)	1 (11.1)	
Size of the thrombus (mm): median [IQR]	60 [30-100]	7 [1-10]	40 [10-50]	59 [30-100]	100 [60-100]	0.032
Mortality – n (%)	5 (11.9)	0 (0)	0 (0)	2 (18.2)	3 (33.3)	0.062

Abbreviations: IQR, interquartile range; IVC, inferior vena cava; NTC, Neves Thrombus Classification.



**Fig. 1** Overall 5-year survival.

complications, since this type of approach requires sternotomy, clamping of the hepatic hilum or incision of the diaphragm.

In this scenario, the objective of the surgical management is to achieve complete resection of the tumor burden, and this may mean resection of the IVC, vascular reconstruction, retroperitoneal lymphadenectomy or metastasectomy. Currently, the standard of treatment is the open approach; however, minimally-invasive laparoscopic or robot-assisted approaches have been shown to be effective among patients in lower NTC levels with superiority in bleeding, surgical time, transfusion, and hospital stay.<sup>13</sup> However, for level-III patients in whom hepatic vein control, portal circulation and suprahepatic control is necessary, it can be challenging. Nevertheless, there are series<sup>14,15</sup> with level-III patients that demonstrate the feasibility of this type of approach.

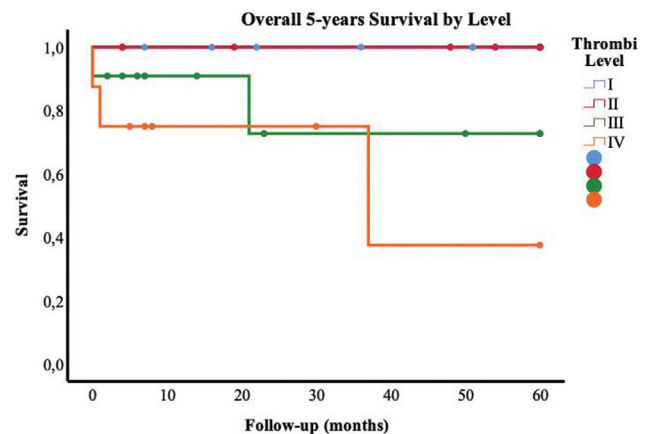
The limitations of the present study included the retrospective evaluation of the database, as well as the small number of patients with VTT, due to its prevalence. However, the strengths include the long follow-up, opening the field to research on level-III patients, reducing even more the mortality when performing thrombectomy, and establishing this surgical procedure as a gold standard.

## Conclusions

The 5-year OS rate was of 100% among level-I and -II patients, with a very low or null rate of complications, establishing nephrectomy with thrombectomy as the first-line management in patients with RCC and VTT. However, among level-III and -IV patients, the mortality is of up to 33%, and it seems to be lower when using transesophageal echocardiogram and extracorporeal bypass as a standard of care during the surgery; thus, we recommend their routine use when performing nephrectomy with thrombectomy in patients with RCC and VTT on NTC levels III and IV.

### Conflict of interests

The authors have no conflict of interests to declare.



**Fig. 2** Overall 5-year survival stratified by level.

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