

# Reduction in Tumor Thrombus After Systemic Treatment for Advanced Renal Cell Carcinoma: A Report of Two Cases and Literature Review

## İlerlemiş Renal Hücreli Karsinomda Sistemik Tedavi Sonrası Tümör Trombüsünde Azalma: İki Olgu Raporu ve Literatür Taraması

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### Abstract

Six percent of cases with renal cell carcinoma (RCC) can present with thrombus, and also invasion to renal vein, and atrium may be observed in 44% and 1-4 % of these cases, respectively. These cases require multidisciplinary management and surgery should be the first treatment option. However, if a tumor is considered unresectable or metastatic, systemic therapy can be considered in the first instance. Herein, we present 2 cases. A 77-year-old female patient presented with right renal tumor 89 mm in diameter with thrombus level IV considerably unresectable started to receive treatment with nivolumab and cabozantinib. After 6 months of treatment thrombus was reduced to level II. A 43-year-old male, presented with 110 mm- right renal mass with thrombus level II and lung metastases. He started to receive pembrolizumab and axitinib. At 6 months of treatment, the size of the tumor and thrombus decreased. In both cases we performed laparoscopic radical nephrectomy with thrombectomy, and pathology reports indicated the presence of clear cell RCC, Grade 3, pT3b-Nx. Systemic treatment in patients with RCC associated with tumor thrombus, whether metastatic or not, would seem to obtain some benefit prior to surgery -line favor surgical feasibility.

**Keywords:** renal cell carcinoma, inferior vena cava, immunotherapy, laparoscopic surgery, thrombosis

### Özet

Renal hücreli karsinomlu (RHK) olguların %6'sı trombüs ile başvurabilir ve ayrıca bu olguların %44'ünde renal ven ve %1-4'ünde atriyum invazyonu görülebilir. Bu vakalar multidisipliner yönetim gerektirir ve cerrahi ilk tedavi seçeneği olmalıdır. Bununla birlikte, tümörün rezekt edilemediği veya metastatik olduğu düşünülüyorsa, ilk etapta sistemik tedavi düşünülebilir. Bu yazıda 2 olgu sunulmuştur. Sağ böbrek tümörü 89 mm çapında, trombüs seviyesi IV olan ve rezekt edilemeyen 77 yaşında bir kadın hasta nivolumab ve cabozantinib tedavisi almaya başladı. Altı aylık tedaviden sonra trombüs seviyesi II'ye düşürüldü. 43 yaşında erkek hasta, 110 mm'lik sağ böbrek kitlesi, trombüs seviyesi II ve akciğer metastazları ile başvurdu. Hastaya pembrolizumab ve aksitinib tedavisi başlandı. Tedavinin 6. ayında tümörün ve trombüsün boyutu azaldı. Her iki vakada da trombektomi ile birlikte laparoskopik radikal nefrektomi uygulandı ve patoloji raporları berrak hücreli RHK, Grade 3, pT3b-Nx varlığını gösterdi.

Metastatik olsun ya da olmasın, tümör trombüsü ile ilişkili RHK'lı hastalarda sistemik tedavi, cerrahi fizibilite lehine cerrahi öncesi bir miktar fayda sağlayacak gibi görünmektedir.

**Anahtar kelimeler:** renal hücreli karsinom, inferior vena kava, immünoterapi, laparoskopik cerrahi, tromboz

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## Introduction

Renal cell carcinoma (RCC) can present with venous thrombus in approximately 6% of cases, and invasion of the renal vein, and extension up to the atrium may be seen in 44%, and 1-4 % of these cases, respectively [1]. Mayo clinic thrombus classification is the most frequently used staging system to decide on feasibility of surgical treatment. Since various treatment methods have been used for level III tumors, Ciancio et al. divided these tumors into 4 sublevels, so as to assess therapeutic challenges and surgical feasibility in the management of these tumors [2]. Multidisciplinary management is required from both clinical and surgical perspectives, and the surgical intervention is the first option in these patients [3].

Systemic treatment should be considered as a first-line alternative if a metastatic or unresectable RCC is present [4]. We have described 2 cases and reviewed the available literature up to February 2024.

## Case Presentations

### Case 1

Magnetic resonance imaging (MRI) of a 77-year-old asymptomatic woman with a history of diabetes, hypertension and hypothyroidism with unremarkable laboratory test results revealed a contrast-enhanced mass on her right kidney measuring 89 x 77 mm, with tumor vascular compromise, and a RENAL nephrometry score of 12 ph. This mass lesion invaded the renal vein and inferior vena cava (IVC), extending from the renal hilum to the right atrium (**Figure 1a**). No lesion was detected on chest tomography.

A multidisciplinary evaluation determined that it was a non-metastatic RCC with level IV tumor thrombus, and the patient was not considered for surgery due to compromise of the intrahepatic venous wall. Renal biopsy findings were reported as RCC, clear cell variety then systemic treatment was started with nivolumab and cabozantinib. After 12 well tolerated treatment sessions applied twice a month, MRI was performed which showed a decrease in the tumor size (54.8 x 48.3 x 43 mm), and a RENAL nephrometry score of 8ph. Additionally a decrease in the size of the tumor thrombus was evident to level II (**Figure 1b**). After 9 months of systemic treatment, we decided to perform laparoscopic right radical nephrectomy with inferior vena cava thrombectomy.

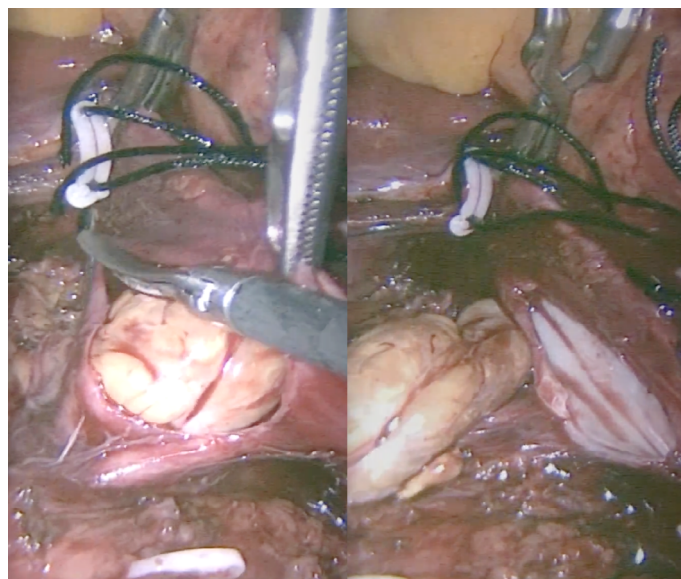
Early ligation of the right renal artery in aortic intercaval space was performed. Right renal vein was identified with a tumor thrombus that penetrated about 2 centimeters into the IVC. We first dissected and then clamped the IVC in its cephalic and caudal portions, and the left renal vein. Dissection of the right renal vein was extended to the vena cava (**Figure 2**). Tumor thrombus was extracted from the vena cava and cavorrhaphy was performed and then the clamps were released. Finally, the kidney was completely freed and extracted through an incision in the right iliac fossa.

There was no postoperative complications, i.e. drop in hemoglobin or hematocrit levels and a creatinine level of 1 mg/dL was maintained. She was discharged 3 days after surgery.

The histopathological report indicated clear cell RCC,



**Figure 1.** a: MRI images of case 1 before systemic treatment; b: MRI images of case 1 after systemic treatment



**Figure 2.** Intraoperative images of case 1

ISUP Grade 3 with renal sinus invasion and infradiaphragmatic tumor thrombus, TNM: pT3b-Nx-Mx. Adjuvant treatment with pembrolizumab was proposed, which was suspended at the 2nd dose due to the drug intolerance of the patient. So far, we haven't got any information concerning 20 months of her follow-up.

### Case 2

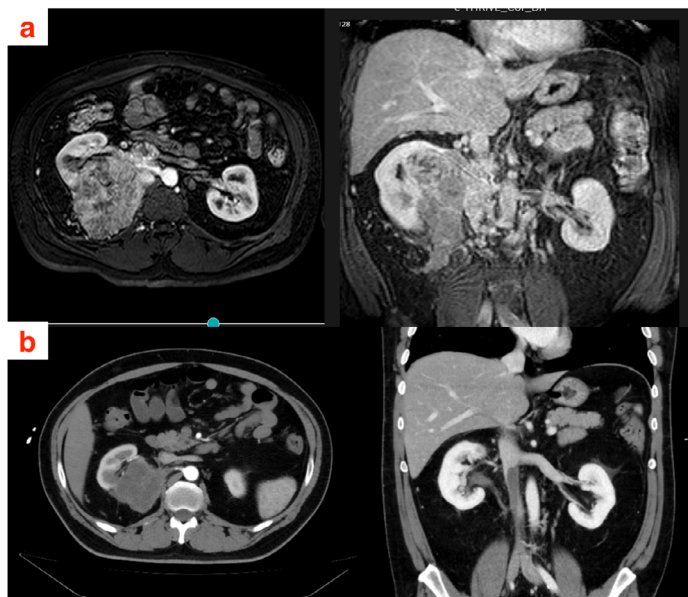
A 43-year-old male patient came to our center with hematuria and discomfort in the right testicle. The physical examination revealed a right varicocele, so an ultrasound of the testicles and abdomen was requested, which revealed a renal mass.

Computed tomography (CT) revealed a right renal mass measuring 110 x 100 x 130 mm that infiltrated the renal sinus, and displaced the ureter. CT also displayed thrombus in the infrarenal vena cava, while infiltration of the vein wall could not be confirmed.

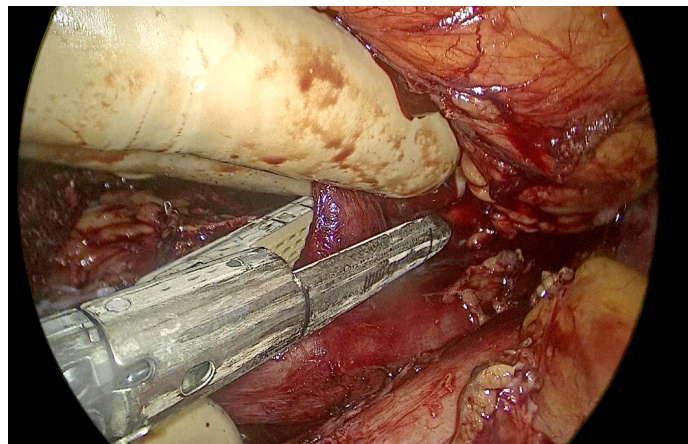


In the thorax, a 20 x 18 mm nodular image was seen in the left lower lung lobe, and other small nodular images in the middle lobe of the left lung were observed, as well. An MRI was requested which confirmed the presence of a right renal mass that is in contact with and infiltrated the IVC through its posterior wall with endoluminal thrombus below the renal veins that reached the confluence of the iliac branches (**Figure 3a**).

Renal biopsy result was renal cell carcinoma, clear cell variety. Metastatic RCC with tumor thrombus was considered. Its International Metastatic RCC Database Consortium (IMDC) risk score was intermediate risk +1. Pembrolizumab + axitinib was started at that time with a good response. At that time the patient also started to receive anticoagulant therapy with low molecular weight heparin. After 6 months of systemic treatment, we decided on a new control CT scan, observing a great decrease in the tumor mass, with no evidence of compromise of the IVC wall and thrombus persisting without changes in the infrarenal IVC and lumbar vein (**Figure 3b**). Then we decided to perform laparoscopic right radical nephrectomy with thrombectomy of the IVC.



**Figure 3.** a: CT images of case 2 before systemic treatment; b: CT images of case 2 after systemic treatment



**Figure 4.** Intraoperative image of case 2

Dissection of the inferior vena cava until the right renal pedicle was located, which was firmly attached to all planes. The renal vein was evident with a thrombus that reached up to the orifice of IVC. In addition, another red thrombus was evident in the vena cava that extended from the orifice of the gonadal vein to approximately the bifurcation of the iliac veins; We decided to perform a nephrectomy without intervening the red thrombus. Ligation of the renal arteries was performed. The kidney remained firmly adhered to the psoas muscle, so we decided to remove the thrombus from the renal vein with manual assistance without resorting to surgery, and the defect on the renal vein was repaired with sutures (**Figure 4**). Extraction of the specimen was performed through the manual assistance device.

There was no postoperative complications, and he was discharged 3 days later with anticoagulation. The histopathological report indicated clear cell RCC, ISUP: Grade 3 with extensive invasion of the capsule, renal sinus and renal vein, TNM: pT3b-Nx.

He currently continues treatment with pembrolizumab and axitinib with good tolerance without disease progression during 18 months of follow-up.

## Discussion

RCC with thrombus in the IVC should be managed surgically as a first alternative with an established benefit in overall survival [5]. There is a high degree of controversy about the extension of the thrombus and the prognosis. Wagner et al. indicated that if the thrombus extends into the vena cava, survival is worse compared to thrombi located only in the renal vein within the context of other factors specific to the patient and anatomopathological characteristics [6].

The vein wall invasion with thrombi should be evaluated by its surgical prognostic value, since the invasion of the vein wall entails longer surgical time, more profuse bleeding, and higher rate of transfusions. If it requires a minimally invasive approach, there will be a higher conversion rate [7]. Therefore, clinical and surgical planning is a fundamental step in these patients, even more so when systemic therapies are taking a leading role in the treatment of these complex cases [8], where a multidisciplinary assessment is essential to determine whether it is resectable, unresectable, locally advanced or systemic treatment should be offered in the first instance [4]. Accordingly, several retrospective studies have inquired whether or not systemic therapy with vascular endothelial growth factor receptor tyrosine kinase inhibitors had a benefit in reducing the level of thrombus. The results were encouraging. Indeed, when sunitinib, sorafenib or axitinib were used, 25 - 28% reduction in the size of thrombi was achieved [9,10]. Stewart et al. presented a phase 2 study where they reported 8 weeks of treatment with axitinib to assess its safety, efficacy and neoadjuvant effect in the management of venous tumor thrombus with an overall response rate of 35 percent [11]. There are reports where the use of immunotherapy with immune checkpoint inhibitors (ICI) in combination with tyrosine kinase inhibitors (TKI) seems to be useful as preoperative therapy in these cases that can be classified as inoperable in the first instance [12–14]. If the disease is metastatic, the risk should be quantified, and also the appropriate time to perform cytoreductive nephrectomy should be assessed according to the

IMDC criteria. The recommendation for systemic treatment, after biopsy of the primary or a metastatic site, is the use of ICI together with a TKI in intermediate and high-risk patients [15].

The strength of this report is the fact that it investigated rarely used neoadjuvant therapy, and its role in improving surgical results in cases with RCC associated with venous thrombi. Since availability of scarce literature data that support downstaging using neoadjuvant therapy in these cases, we could not formulate a management protocol for these cases.

Systemic treatment in patients with RCC associated with IVC tumor thrombus, whether metastatic or not, would seem to provide some benefit prior to surgery and favor surgical feasibility. However, further prospective studies should be performed to determine the real benefit of this approach.

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## References

- [1] Jurado A, Romeo A, Gueglio G, Marchiñena PG. Current Trends in Management of Renal Cell Carcinoma with Venous Thrombus Extension. *Curr Urol Rep*. 2021;22(4):23. <https://doi.org/10.1007/s11934-021-01036-y>
- [2] Ciancio G, Vaidya A, Savoie M, Soloway M. Management of renal cell carcinoma with level III thrombus in the inferior vena cava. *J Urol*. 2002;168(4 Pt 1):1374–7. [https://doi.org/10.1016/S0022-5347\(05\)64452-7](https://doi.org/10.1016/S0022-5347(05)64452-7)
- [3] Lardas M, Stewart F, Scrimgeour D, Hofmann F, Marconi L, Dabestani S, et al. Systematic Review of Surgical Management of Nonmetastatic Renal Cell Carcinoma with Vena Caval Thrombus. *Eur Urol*. 2016;70(2):265–80. <https://doi.org/10.1016/j.eururo.2015.11.034>
- [4] Ljungberg B, Albiges L, Abu-Ghanem Y, Bedke J, Capitanio U, Dabestani S, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 Update. *Eur Urol*. 2022;82(4):399–410. <https://doi.org/10.1016/j.eururo.2022.03.006>

- [5] Huned D, Carsen JA, Huang HH, Lee LS. The incremental benefit of upfront surgery in renal cell carcinoma with venous tumor thrombus of the inferior vena cavae. *Urol Sci*. 2018;29(6):277–83. [https://doi.org/10.4103/UROS.UROS\\_31\\_18](https://doi.org/10.4103/UROS.UROS_31_18)
- [6] Wagner B, Patard JJ, Méjean A, Bensalah K, Verhoest G, Zigeuner R, et al. Prognostic value of renal vein and inferior vena cava involvement in renal cell carcinoma. *Eur Urol*. 2009;55(2):452–9. <https://doi.org/10.1016/j.eururo.2008.07.053>
- [7] Zhao X, Yan Y, Dong JH, Liu Z, Zhang HX, Liu C, et al. Influence of Deep Invasive Tumor Thrombus on the Surgical Complexity and Prognosis of Patients With Non-Metastatic Renal Cell Carcinoma Combined With Venous Tumor Thrombus. *Front Oncol*. 2022;12:833780. <https://doi.org/10.3389/fonc.2022.833780>
- [8] Muselaers S, Mulders P, Bertolo R, Erdem S, Ingels A, Marandino L, et al. Inferior vena cava involvement in renal cell carcinoma: if you fail to plan, you're planning to fail. *Minerva Urol Nephrol*. 2021;73(6):854–7. <https://doi.org/10.23736/S2724-6051.21.04811-4>
- [9] Tanaka Y, Hatakeyama S, Hosogoe S, Tanaka T, Hamano I, Kusaka A, et al. Presurgical axitinib therapy increases fibrotic reactions within tumor thrombus in renal cell carcinoma with thrombus extending to the inferior vena cava. *Int J Clin Oncol*. 2018;23(1):134–41. <https://doi.org/10.1007/s10147-017-1169-z>
- [10] Peng C, Gu L, Wang L, Huang Q, Wang B, Guo G, et al. Role of presurgical targeted molecular therapy in renal cell carcinoma with an inferior vena cava tumor thrombus. *Onco Targets Ther*. 2018;11:1997–2005. <https://doi.org/10.2147/OTT.S158114>
- [11] Stewart GD, Welsh SJ, Ursprung S, Gallagher FA, Jones JO, Shields J, et al. A Phase II study of neoadjuvant axitinib for reducing the extent of venous tumour thrombus in clear cell renal cell cancer with venous invasion (NAXIVA). *Br J Cancer*. 2022;127(6):1051–60. <https://doi.org/10.1038/s41416-022-01883-7>
- [12] Hara T, Terakawa T, Hyodo T, Jinbo N, Nakano Y, Fujisawa M. Pathological complete response of renal cell carcinoma with vena cava tumor thrombus to neoadjuvant TKI/IO combination therapy. *Urol Case Rep*. 2021;39:101800. <https://doi.org/10.1016/j.eur.2021.101800>
- [13] Suzuki I, Kijima T, Takada-Owada A, Nakamura G, Uematsu T, Sakamoto K, et al. A case of clear cell renal cell carcinoma with vena cava thrombus responding to presurgical avelumab, and axitinib. *IJU Case Rep*. 2021;4(6):412–6. <https://doi.org/10.1002/iju5.12362>

- [14] Uematsu T, Kijima T, Takada-Owada A, Nishihara D, Ishida K, Kamai T. Presurgical avelumab plus axitinib in an immunosenescent octogenarian with renal cell carcinoma invading the vena cava. *Urol Case Rep.* 2022;45:102205. <https://doi.org/10.1016/j.eucr.2022.102205>
- [15] Yoshida K, Hata K, Iizuka J, Kondo T, Ishihara H, Ishida H, et al. Immune Checkpoint Inhibitor Combination Therapy for Renal Cell Carcinomas With Concomitant Inferior Vena Cava Thrombi. *In Vivo.* 2022;36(2):1030–4. <https://doi.org/10.21873/invivo.12798>