

Mid-term results of surgical interventions of high-grade vena cava tumor thrombus

Yüksek dereceli vena cava tümör trombusünde cerrahi müdahalelerin orta dönem sonuçları

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ABSTRACT

Background: This study aims to investigate whether the coexistence of advanced renal cell carcinoma and inferior vena cava tumor thrombus could be treated with a multidisciplinary approach and teamwork and to evaluate early and mid-term results.

Methods: Between January 2017 and December 2020, a total of 33 patients (28 males, 5 females; mean age: 55.8±13.2 years; range, 27 to 76 years) who underwent radical nephrectomy and thrombectomy of the inferior vena cava were retrospectively analyzed. Demographic characteristics of the patients, types of operations, postoperative data, mortality and morbidity rates were recorded.

Results: Of the patients, 12% (n=4) had Stage 2 tumor thrombus, 60.6% (n=20) had Stage 3 tumor thrombus, and 27% (n=9) had Stage 4 tumor thrombus. A total of 55% (n=19) of the patients had right-sided renal cell carcinoma, while 45% (n=14) of them had a left-sided mass. Totally, 66% (n=22) of the patients underwent primary inferior vena cava repair. The thrombectomy procedure and a Dacron® patch was applied with patch plasty in 24% (n=8) of the patients, and Dacron® graft interposition was applied to the inferior vena cava in 9% (n=3) of the patients. The mean follow-up was 20.3±13.0 (range, 2 to 70) months. Deep vein thrombosis was detected in the follow-up of seven (21%) patients, and no pulmonary thromboembolism was observed during the postoperative follow-up period. The mean length of stay in the intensive care unit was 1.39±0.6 (range, 1 to 3) days. The 30-day mortality rate was 3%, due to the loss of one patient from massive pulmonary embolism intraoperatively.

Conclusion: Vascular surgical procedures performed regardless of the stage of the tumor thrombus provide satisfactory mid-term results in patients with advanced renal cell cancer.

Keywords: Cardiopulmonary bypass, renal cell carcinoma, thromboendarterectomy, vena cava.

ÖZ

Amaç: Bu çalışmada, renal hücreli karsinom ve inferior vena cava tümör trombus birlikteliğinin multidisipliner bir yaklaşım ve ekip çalışması ile tedavi edilip edilemeyeceği araştırıldı ve erken ve orta dönem sonuçları değerlendirildi.

Çalışma planı: Ocak 2017 - Aralık 2020 tarihleri arasında, radikal nefrektomi ile birlikte inferior vena kavaya trombektomi uygulanan toplam 33 hasta (28 erkek, 5 kadın; ort. yaş: 55.8±13.2 yıl; dağılım, 27-76 yıl) retrospektif olarak incelendi. Hastaların demografik özellikleri, ameliyat türleri, ameliyat sonrası verileri, mortalite ve morbidite oranları kaydedildi.

Bulgular: Hastaların %12'sinde (n=4) Evre 2 tümör trombusü, %60.6'sında (n=20) Evre 3 tümör trombusü, %27'sinde (n=9) Evre 4 tümör trombusü vardı. Hastaların toplam %55'inde (n=19) sağ taraflı renal hücreli karsinom ve %45'inde (n=14) sol taraflı kitle mevcuttu. Hastaların toplam %66'sında (n=22) inferior vena cava primer olarak onarıldı. Hastaların %24'üne (n=8) trombektomi ve yama plasti ile Dacron® yama uygulandı ve %9'una (n=3) inferior vena kavaya Dacron® greft interpozisyonu yapıldı. Ortalama takip süresi 20.3±13.0 (dağılım, 2-70) ay idi. Yedi (%21) hastanın takibinde derin ven trombozu saptandı ve ameliyat sonrası takip döneminde pulmoner tromboemboli saptanmadı. Yoğun bakım ünitesinde ortalama kalış süresi 1.39±0.6 (dağılım, 1-3) gün idi. Bir hasta ameliyat sırası masif pulmoner tromboemboli nedeniyle kaybedildiği için 30 günlük mortalite oranı %3 idi.

Sonuç: İleri evre renal hücreli kanser hastalarında tümör trombusünün evresinden bağımsız olarak yapılan vasküler cerrahi işlemler tatmin edici orta vadeli sonuçlar sağlar.

Anahtar sözcükler: Kardiyopulmoner baypas renal hücreli karsinom, tromboendarterektomi, vena cava.

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Renal cell carcinoma (RCC) is a malignant disease that invades the inferior vena cava (IVC). Tumor invasion of the IVC occurs in approximately 4 to 10% of RCC patients and is associated with a poor prognosis.^[1] The average survival time in patients with RCC with untreated IVC invasion is about six months,^[2] and tumor thrombectomy to IVC increases survival.^[3] The treatment method in RCC cases with IVC invasion is radical nephrectomy (RN) and IVC thrombectomy.^[4] Both methods are technically challenging procedures with high complication rates and a 10% intraoperative mortality.^[5]

The thrombectomy procedure performed in cases of IVC invasion may vary according to the stage of the tumor thrombus. While ligation of only the renal vein may be sufficient in early-stage patients, since tumor thrombus extends from the IVC to the right atrium in advanced-stage patients; it may be even necessary to use cardiopulmonary bypass (CPB). Therefore, a multidisciplinary approach is required in complicated and advanced patients.

In the present study, we aimed to investigate whether the coexistence of advanced RCC and IVC tumor thrombus could be treated with a multidisciplinary approach and teamwork and to evaluate early and mid-term results.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Marmara University Pendik Training and Research Hospital, Department of Cardiovascular Surgery between January 2017 and December 2020. A total of 138 patients who were operated for RCC were analyzed. The data of the patients were obtained from hospital automation system and medical records.

Computed tomographic angiography (CTA) was performed in all patients during the preoperative period to localize the tumor and identify the stage of the IVC tumor thrombus. Patients were graded according to Neves classification.^[6] Since the treatment of Stage 0 and Stage 1 patients was only nephrectomy, 105 patients in this group were excluded from the study. Finally, a total of 33 patients (28 males, 5 females; mean age: 55.8±13.2 years; range, 27 to 76 years) with Stage 2-4 tumor thrombus were included. Patients in Stage 2, 3, 4 group were compared in terms of demographic characteristics, types of operations, postoperative characteristics, mortality and morbidity. Preoperative anticoagulation was provided with enoxaparin as recommended dosages. In patients who had primary IVC repair or Dacron® patch plasty, enoxaparin treatment was

continued and acetylsalicylic acid was administered as 100 mg per day at the postoperative period. Patients with tubular Dacron® graft interposition to the IVC were also treated with warfarin during follow-up. Postoperative International Normalized Ratio (INR) was ranged between 2.5 and 3.5. All patients received eligible chemotherapy protocols, at the discretion of the Department of Oncology.

Surgical procedures

All patients were operated under general anesthesia. An upper midline incision, Chevron incision, or a median laparotomy incision was preferred based on the surgeon's preference, tumor location, and thrombus stage. Radical nephrectomy was performed first in all patients.

Stage 2

In patients with Stage 2 tumor thrombus, thrombectomy was performed without systemic heparinization with the help of partial side-clamps, and the venotomy in the vena cava was repaired using 5-0 Prolene sutures in a continuous suture technique.

Stage 3

Patients with Stage 3 tumor thrombus underwent transesophageal echocardiography (TEE) which can fully evaluate the IVC and cardiac functions. After RN, surgical bleeding was controlled at the tumor site and patients were systemically heparinized at a dose of 100 IU/kg. Heparin activity according to the activated clotting time (ACT) (Hemochron Signature, Instrumentation Laboratory, MA, USA) was measured and held for at least 200 sec. If the ACT levels were sufficient, the suprahepatic segment of the IVC was reached by releasing the liver and, initially, a clamp was inserted into the suprahepatic IVC to prevent pulmonary embolism. After clamping the proximal IVC, the clean distal IVC without the tumor thrombus that was detected using the preoperative CTA and TEE was clamped. Subsequently, there was a waiting time of at least 1 min for adequate venous return and hemodynamic stability. After the venotomy, endarterectomy was performed to the IVC and in suitable patients, the IVC was repaired using 5-0 Prolene sutures. In three patients, adequate tumor excision was not achieved through the RN; therefore, in these patients the tumor that was invading the IVC wall was excised along with the intact part, and the IVC was repaired with tubular Dacron® graft interposition (Figure 1). In eight patients, a patch plasty was applied with a Dacron® patch, considering that, with the repair of

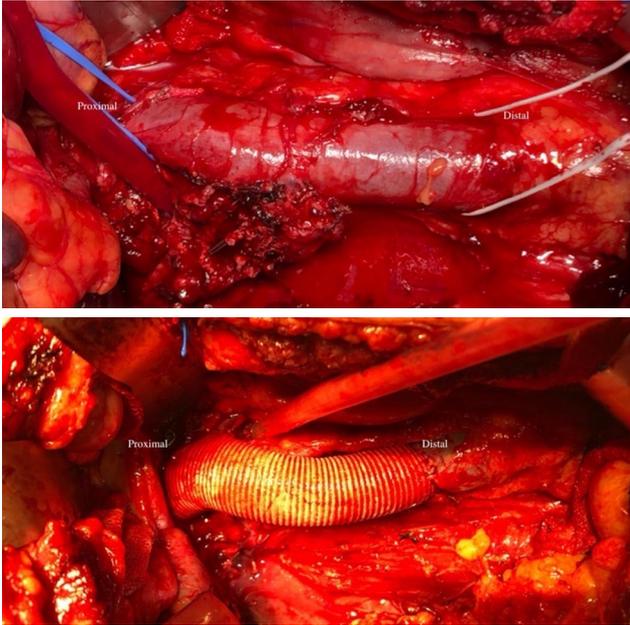


Figure 1. Dacron® graft was interposed to inferior vena cava due to inadequate tumor resection.

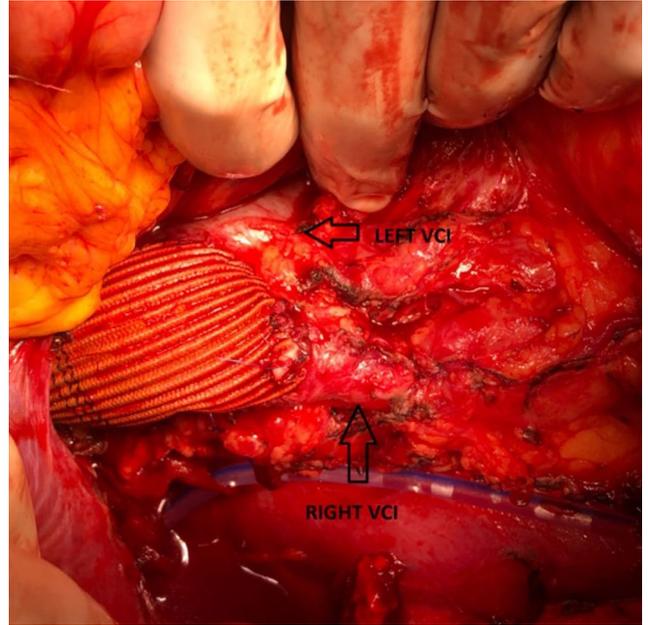


Figure 2. Patch plasty of inferior vena cava with a Dacron® patch in a patient with dual inferior vena cava.

the defect, more than 50% stenosis could occur in the lumen of the IVC (Figure 2).

Stage 4

Transesophageal echocardiography was performed in patients during the preoperative preparation stage for adequate venous cannulations in the course of the CPB and the preoperative visualization of the IVC. The renal mass was explored in preparation for the RN in the involved area, and the renal artery and renal vein were ligated. The renal mass was kept in an avascular state. Then, a median sternotomy was performed and patients were heparinized at a dose of 300 IU/kg. In five patients with Stage 4 tumor thrombus, the tumor thrombus invaded only the right atrium and there was no thromboembolic material in the pulmonary arteries. In these patients, arterial cannulation for CPB was performed from the aorta, venous cannulation was performed from the femoral vein and the superior vena cava (SVC) on the side without the tumor. With the help of the TEE, it was checked that the venous cannula in the femoral vein was not placed in the IVC. Cardiac arrest was performed with the appropriate dose of antegrade blood cardioplegia and a right atriotomy was performed. While the tumor thrombus in the right atrium-IVC junction was excised, the thrombi that were unable to be reached by venotomy to the suprarenal IVC were also cleaned. In addition, TEE was performed to check and visualize the opening

of the hepatic veins and if there was any remaining thrombus residue in the IVC (Figure 3).

Four patients with Stage 4 tumor thrombus had both right atrial tumor thrombus and pulmonary thromboembolism (PTE), which is very rare in RCC (Figure 4). In these patients, arterial cannulation was performed from the right axillary artery instead of the aorta, to minimize the aortic manipulations during the right pulmonary artery thrombectomy and seeking for a better surgical view were the main reasons for this choice. Venous cannulation was performed in the same way from the femoral vein and the SVC. After the cardiac arrest was obtained using antegrade blood cardioplegia, initially, arteriotomy to the main pulmonary artery along with thrombectomy to the pulmonary artery was performed after clearing the tumor thrombus in the IVC with the right atriotomy. Mean circulatory arrest time was 18 (range, 17 to 22) min and all patients were cooled to 28°C.

Near-infrared spectroscopy was used to monitor cerebral oxygenation (INVOS Cerebral Oximeter, Somanetics, MI, USA) during circulatory arrest period. Ice was placed around the patient's head and intravenous methylprednisolone 1 g was administered for brain protection.

Pulmonary thrombectomy would be also performed and the aorta would be manipulated

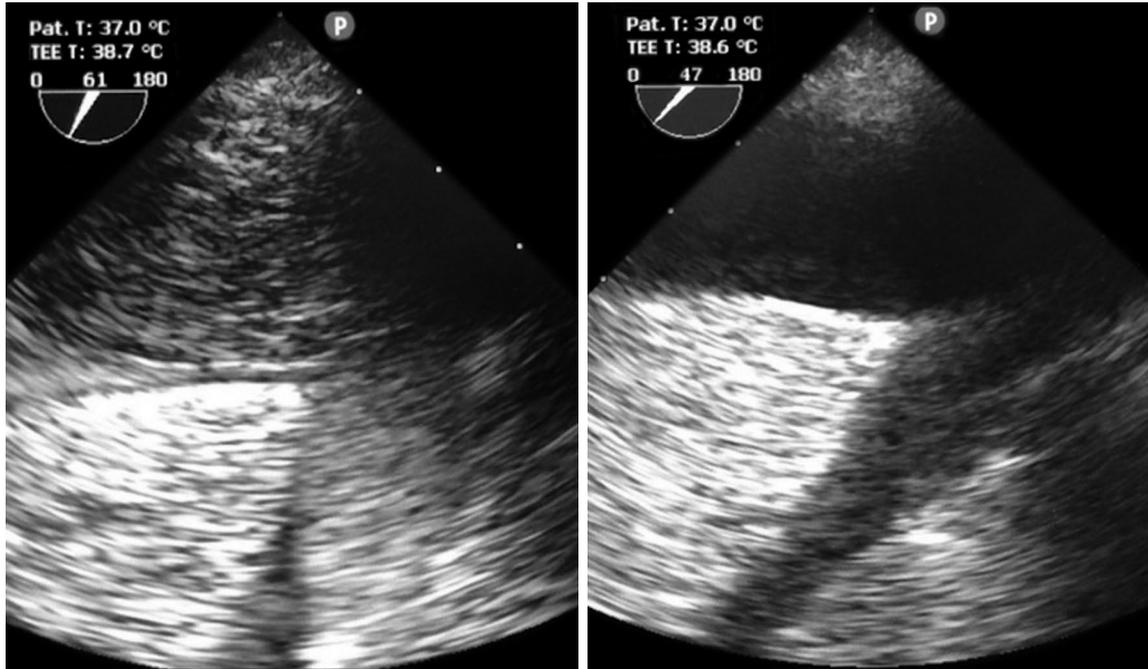


Figure 3. Transesophageal echocardiographic image of a tumor thrombus in inferior vena cava.

while reaching the right pulmonary artery during the thrombectomy. All pulmonary thromboendarterectomies were performed at the level of main pulmonary artery and arteriotomy incision was continued to the left and right pulmonary arteries. Pathological findings were interesting, one specimen contained thrombotic material only, two

specimen consisted of mixed tumoral and thrombotic cells and only one specimen included tumoral cells.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in



Figure 4. Computed tomographic image of a tumor thrombus in pulmonary artery.

Table 1. Demographic and clinical data of the patients

	Stage 2 (n=4)			Stage 3 (n=20)			Stage 4 (n=9)			p
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			59.0±6.1			52.5±14.7			61.7±9.9	0.19
Sex										0.58
Male	3	9.1		18	54.5		7	21.2		
Female	1	3		2	6.1		2	6.1		
Tumor diameter (cm)			10.6±1.8			11.7±2.7			10.9±2.7	0.08
Coronary artery disease				4	12.1		1	3		0.55
Diabetes mellitus	1	3		5	15.2		1	3		0.68
Hypertension	2	6.1		8	24.2		7	21.2		0.16
Preoperative creatinine (mg/dL)			0.9±0.2			1.1±0.3			0.9±0.3	0.29
Postoperative creatinine (mg/dL)			0.9±0.3			1.2±0.3			1.1±0.3	0.21

SD: Standard deviation.

mean ± standard deviation (SD), while categorical variables were expressed in number and frequency. The chi-square and Fisher exact chi-square tests were used in cross-table analyses. Normality distribution of the data was analyzed using the Kolmogorov-Smirnov test. Whether there was a difference among the three groups in terms of the measured variables was evaluated by one-way analysis of variance (ANOVA) for parametric data. A *p* value of <0.05 was considered statistically significant.

RESULTS

Demographic data of the patients are presented in Table 1. According to the tumor thrombus stage, there was no statistically significant difference in age, sex, and tumor diameter of the patients.

A total of 12% (n=4) of the patients had Stage 2 tumor thrombus, 60.6% (n=20) had Stage 3 tumor thrombus, 27% (n=9) had Stage 4 tumor thrombus. While 55% (n=19) of the patients had right-sided RCC, 45% (n=14) of them had a left-sided mass. The IVC was repaired primarily in 66% (n=22) of the patients. In 24% (n=8) of the patients, thrombectomy and patch plasty with a Dacron® patch was performed, a tubular Dacron® graft interposition to the IVC was performed in 9% (n=3) of the patients. The mean intraoperative blood loss was 1750±890 mL, and no statistically significant difference was found between these repair methods and the tumor thrombus stage. The mean duration of stay in the intensive care unit was 1.39±0.6 (range, 1 to 3) days.

The mean follow-up was 20.3±13.0 (range, 2 to 70) months. One (3%) patient died during the operation

due to massive pulmonary embolism. Deep vein thrombosis was detected during follow-up of seven patients (21%), and no PTE was detected during the postoperative follow-up period. No statistically significant difference was found between the preoperative urea and creatinine values and the postoperative urea and creatinine values of the patients. No complications such as wound infection, bacteremia, or septicemia were encountered.

While the 30-day mortality was 3% due to the loss of one patient from intraoperative massive pulmonary embolism, in-hospital mortality was not found in other patients. Mortality was not observed in any of the patients during the postoperative follow-up period.

DISCUSSION

Renal cell carcinoma is one of the 10 most common cancer types in both sexes and the lifetime risk of developing RCC is 1.6%.^[7]

Radical nephrectomy and IVC thrombectomy increases the survival in patients with both advanced RCC and IVC tumor thrombus and is currently the recommended treatment method.^[8,9] However, the combination of these two procedures may lead to complications, such as massive PTE, which may occur as a result of mobilization of the tumor, particularly during thrombectomy. In various case series, the first 30-day mortality of RN and IVC thrombectomy was found to be around 1.5 to 10%.^[10] In our series, one patient in the Stage 3 group died due to intraoperative massive pulmonary embolism. While no mortality was detected in the first 30 days in the remaining 32 patients.

Depending on the level of the tumor thrombus, complication rates after RN and IVC thrombectomy have been found in the literature to be around 30%.^[8-10] In our case series, prolonged ventilation developed in nine (27%) patients, regardless of the tumor thrombus stage, and deep vein thrombosis developed in seven (20.5%) patients during their postoperative follow-up, which was accepted as a postoperative complication. Undoubtedly, undesirable complications, such as bleeding, rupture, or massive PTE, that may occur during IVC thrombectomy reduce the success of the surgery and directly affect survival.

Another controversial aspect of RN and IVC thrombectomy, along with the surgical risk, is its effect on survival. Discussions on this subject have been continuing since Berg performed the first RN and IVC thrombectomy.^[10] There are researchers in the literature who argue that RN and IVC thrombectomy is associated with mid-term survival.^[11] However, Master *et al.*^[12] showed that RN and IVC thrombectomy was associated with long-term survival, and it was also reported that adjuvant treatment with tyrosine kinase inhibitors after surgery prolonged survival.^[13] In our study, no mortality was observed during the follow-up period.

According to the Neves classification, the ligation and the division of the renal vein and the excision of the thrombus is possible and there is no need for additional vascular surgery. Therefore, patients in this group were not evaluated in this study. The approach to treat patients with Stage 2 or higher-grade tumor thrombus was decided as a result of the Councils jointly organized by the Urology and Cardiovascular Surgery clinics of our hospital. While the tumor thrombus was excised with the help of partial side-clamps in patients with Stage 2 tumor thrombus, it was better tolerated hemodynamically, due to less blood loss and no complete occlusion in the IVC.

Hemodynamic stability was more difficult to achieve in patients with Stage 3 tumor thrombus, as in IVC thrombectomy, clamping of the IVC from the suprahepatic section causes total occlusion and there is more blood loss during thrombectomy. However, in these patients, hemodynamic status was stabilized by providing adequate hydration before thrombectomy and, if necessary, erythrocyte replacement or colloid replacement and adequate intravascular volume were also provided. Vasopressor therapy was performed in cases with a mean arterial pressure below 65 mmHg, despite the adequate volume replacement. In Stage 4 patients, the use of CPB provided a much more comfortable hemodynamic control.

Repair of the vena cava after thrombectomy is another challenging issue. The defect that may occur after the RN and venotomy can be challenging, particularly due to the invasion of the tumor into the vena cava wall. While the venotomy was repaired with a Dacron® patch in eight patients in our study, Dacron® graft interposition was applied in three patients with a circular invasion of the vena cava wall or with a complete disruption of the wall integrity.

In the literature, studies have shown that vena cava ligation may be a surgical option in such cases.^[14] However, in this study, patients who underwent vena cava ligation in the early postoperative period had higher complication rates and were re-admitted to the hospital more frequently. Considering that RN and IVC thrombectomy have a high effect on mid- and long-term survival in RCC patients, independent of the metastasis, we believe that this period should be spent without any complication and re-admission to the hospital.

Surgical treatment of Stage 4 patients with tumor thrombus invading the right atrium is possible with the use of CPB. Similarly, in our study, eight patients with Stage 4 tumor thrombus were operated under CPB.

Pulmonary tumor thromboembolism is a rare clinical condition that can be seen in patients with high-grade tumor thrombus and its incidence is 0.9%.^[15] The treatment in patients with PTE is pulmonary endarterectomy accompanied by thrombectomy to IVC.^[15] Chronic exposure of the pulmonary artery to tumor thrombus in these patients leads to inflammation and fibrosis in the vascular bed and may lead to the conversion of the surgical treatment to pulmonary endarterectomy rather than pulmonary embolectomy.^[16] According to the European Association of Urology Guidelines on RCC 2019 update, the role of IVC filters remain uncertain.^[17]

Although deep hypothermic circulatory arrest is used in patients with pulmonary tumor thrombus, according to our experience, pulmonary endarterectomy can be safely performed with moderate hypothermia (28°C) to avoid undesirable side effects of hypothermia in such highly fragile patients. In our study, pulmonary endarterectomy was also performed under moderate hypothermia under CPB for simultaneous pulmonary tumor thromboembolism in four patients with an average of 18 min hypothermia time.

The coexistence of RCC and IVC tumor thrombus is associated with poor prognosis and short survival time. Adjuvant chemotherapy used in conjunction

with surgical treatment increases survival. It has also been shown that, regardless of the stage of the tumor thrombus, these difficult cases may have a better prognosis with a multidisciplinary approach and teamwork.^[12]

We also believe that the preoperative evaluation of these patients should be conveyed with the shared wisdom of urology, vascular surgery, and anesthesiology clinics, the collaborative preparation of the operation road map, and the use of preoperative detailed imaging methods (computed tomography) directly affects intraoperative mortality and morbidity.

The single-center, retrospective design without a control group is the main limitation to this study.

In conclusion, surgical treatment of patients with advanced renal cell carcinoma and inferior vena cava tumor thrombus is associated with near-perfect mid-term survival. Preoperative detailed grading and the choice of more complex procedures according to the grade of the tumors may prolong the survival of patients.

Ethics Committee Approval: The study protocol was approved by the Marmara University Faculty of Medicine Ethics Committee (No: 09.2021.1024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: This study is retrospective and there was no need to obtain written informed consent from patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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