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Original Article

Surgical management of renal cell carcinoma with associated tumor thrombus extending into the inferior vena cava: A 10-year single-center experience

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ABSTRACT

Objective: Renal cell carcinoma (RCC) is a tumor that has a tendency of vascular invasion by extending to the inferior vena cava (IVC) after the renal vein. The total resection of the renal tumor and tumor thrombus is considered the optimal treatment. In our study, we aimed to present the results related to 34 consecutive cases of RCC with tumor thrombus.

Material and methods: Of the 442 patients diagnosed with renal tumors between January 2008 and January 2018, 34 (7.6%) had tumor thrombus over the renal vein extending to the IVC. The data of the 34 patients with tumor thrombus were retrospectively reviewed and included in the study. All the 34 patients underwent radical nephrectomy with tumor thrombectomy. The presence of thrombus was evaluated using contrast-enhanced abdominal tomography, magnetic resonance imaging, or color Doppler ultrasonography. The level of thrombus was classified using the Mayo Clinic tumor thrombus classification. Surgery was performed transperitoneally through a modified Chevron incision and mostly in collaboration with other clinics. Complications were classified according to the Clavien system.

Results: Of the 34 patients, 22 were males and 12 were females. The mean follow-up period was 36±27.2 months in patients who had a mean age of 61±10.9 years. The mean tumor size was 10.5±3.3 cm. The number of patients according to the thrombus levels I, II, and III were 20, 9, and 5, respectively. The average blood loss was 744±285.4 mL. Radical surgery for all patients who had direct invasion to the vena cava wall and/or level II and III was performed by gastrointestinal and cardiothoracic surgeons. Cardiopulmonary bypass was not performed in any patient. Minor complications (Clavien grades 1-2) were seen in 8 (23.5%) patients, while 2 (5.8%) patients had major complications (Clavien grades 3–5). The mean follow-up period was 36 months (range, 6–72 months). The overall 5-year survival rate was 85.2%.

Conclusion: We think that radical nephrectomy and caval thrombectomy is a safe and effective method in patients with RCC without tumor exceeding the diaphragmatic level. We believe that the surgical success rate can be increased using a multidisciplinary approach in selected cases.

Keywords: Renal cell carcinoma; surgical management; venous tumour thrombus.

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Introduction

Renal cell carcinoma (RCC) is the most prevalent primary renal malignant neoplasm in adults. Due to an increase in high resolution imaging, the incidence of RCC is also raised in recent years. Most of the cases are found incidentally. An important characteristic of RCC is extending to the vascular structures without any metastasis. Venous involvement includes manifestation as tumor thrombus in the renal vein on the affected side and potential extension to the inferior vena cava (IVC) or even the right atrium. Nearly 10% of the patients are known to be predisposed to tumor thrombus in the renal vein or IVC at the time of the diagnosis and more commonly on the right side.[1,2] The extension of the thrombus can reach the right atrium in about 1% cases.[3]

Patients with IVC thrombosis are usually symptomatic, with hematuria being the most common presenting symptom.[4] Flank pain, fatigue, weight loss, total obstruction of the tricuspid valve, and paraneoplastic syndromes can also be noted in patients.[5] The IVC syn-

drome, which causes tachycardia, edema in the lower extremities, varicocele, and pulmonary embolism due to the migration of the thrombus are also observed in patients with IVC thrombosis.[5]

The complete removal of renal tumor and thrombus is considered ideal when no distant metastases are present.[6] A challenging surgical procedure with a multidisciplinary approach is needed in patients with invasive thrombus to IVC. The surgical approach should be selected according to the level of tumor thrombus and primary renal tumor characteristics, such as size, location, regional lymphadenopathy, and aberrant vascular anatomy. The longterm survival of patients in whom total removal is achieved seems to be markedly better compared to those with incomplete resection.[7] The 5-year survival rates for renal tumor progressing to the renal vein or IVC exceeds to 50%.[4] However, vena cava tumor thrombectomy is a difficult procedure associated with a substantial risk of perioperative morbidity, such as abundant blood loss, major blood transfusion, and long hospital stay rate up to 70% and a postoperative mortality rate up to 48%.[8]

In the present study, we have retrospectively reviewed our patients who were diagnosed with RCC leading to IVC tumor thrombosis with different levels and treated using radical nephrectomy and tumor thrombectomy in the last 10 years.

Material and methods

A total of 442 patients with RCC had undergone radical nephrectomy in our clinic from January 2008 to January 2018. Of these, 56 (12.6%) had tumor thrombus growing up to the renal vein and IVC without any distant metastasis and had undergone radical nephrectomy with thrombectomy. After the institutional review board approval, medical records of the patients were retrospectively evaluated using relevant clinical and pathological features and survival rates from the hospital database. All participants were explained regarding the surgical technique and signed informed consent form. The study was conducted in compliance with ethical principles defined in Helsinki Declaration. The exclusion criteria consisted of incomplete records, neoadjuvant target therapy, thrombus extending only into the renal vein (level 0), postoperative early exitus (in 1 week), and lack of vital information. After the application of the exclusion criteria, 34 (7.6%) patients were selected for examination and presented in the study. All patients with RCC and caval thrombus were discussed at an urooncology multidisciplinary team council in our hospital. The existence of the intracaval tumor thrombus has been evaluated using color Doppler ultrasound imaging, contrastenhanced computerized tomography (CT), or magnetic resonance imaging (MRI). The patients underwent standard blood tests, abdominal and chest CT, contrast-enhanced abdominal MRI, and/or bone scintigraphy if needed.

The level of IVC extent was stratified following the categorization of thrombus level according to the Mayo Clinic grading system: level 0, tumor thrombus extended to purely the renal vein; level I, tumor thrombus extending into the IVC to no more than 2 cm above the renal vein; level II, thrombus extending into the IVC to more than 2 cm above renal vein but below the hepatic veins; level III, thrombus extending into the IVC to above the hepatic vein but not to the diaphragm; and level IV, thrombus extending into the supradiaphragmatic IVC or right atrium (Figure 1).[9] The tumor nuclear grade was classified according to the Fuhrman system. Pathological staging was determined according to the 2009 tumor, node, metastasis (TNM) staging system of the American Joint Committee on Cancer.

Operative technique

All patients included in the study were routinely performed radical nephrectomy, tumor thrombectomy, and/or lymph node dissection. All procedures were performed by the same urologic surgeon (H.K.). Surgery was mostly performed via an anterior subcostal or modified Chevron incision depending on operating team's choice and the characteristics of tumor and associated tumor thrombus formation. In general, primarily, IVC was explored and thereafter the lumbar veins and massrelated renal artery was ligated. Level I tumor thrombus was resected through partial IVC occlusion only and was resected without any extensive caval dissection. For the resection of higher than level I, the

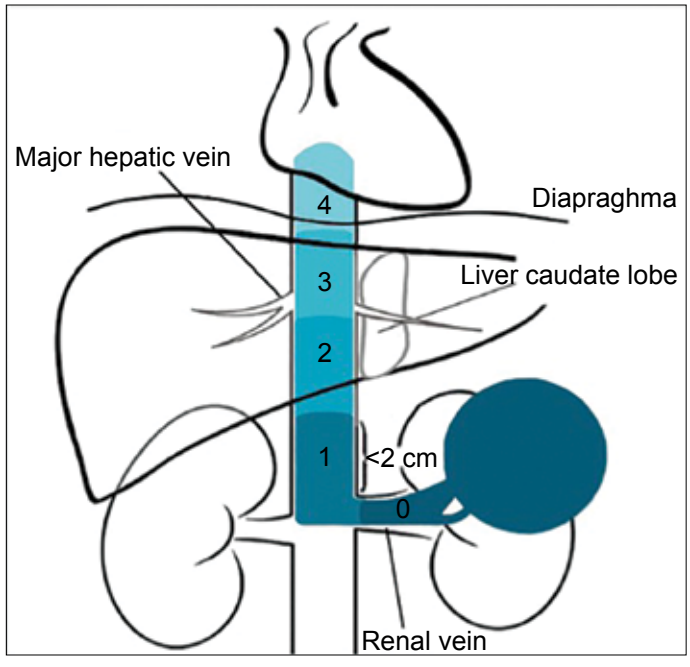

Figure 1. Classification of tumor thrombus level consisting of 4 levels according to the Mayo Clinic staging system

contralateral tumor-free renal vein was dissected and clamped and then the proximal and distal parts of the IVC were clamped before thrombectomy. IVC was opened about the ostium of the renal vein. Caval tumor thrombus was isolated and extracted completely along with the kidney. Complete removal was controlled by checking the totality of the thrombus and entering an index finger to IVC. Cavotomy was closed using double running 5-0 polypropylene sutures. Before complete closure of the IVC, heparinized serum was applied to the lumen, and the distal part of the sutures was closed in the end. This maneuver ensures the remnant clots and the remaining air to be discharged from the IVC. All the procedures were done in collaboration with the departments of gastroenterological surgery and cardiothoracic surgery for above the level I and/or tumor thrombus, which directly invades the IVC wall. All patients were applied 1 mg/kg fractionated heparin daily during postoperative session and at the time of discharge. None of the present patients received routine postoperative adjuvant therapy. Postoperative complications were recorded up to 60 days and categorized according to the modified Clavien system.[10] All cases were assessed for postoperative recurrence and general condition by physical examinations, blood count, blood biochemistry analysis, and chest and abdominal CTs at 3, 6, and 12 months after surgery and yearly thereafter.

Statistical analysis

The data were entered in the statistics program. Statistical analysis tests were performed using the Statistical Package for the Social version 17.0 for Windows (SPSS Inc.; Chicago, IL, USA). All survival rates were calculated using the Kaplan–Meier method. As descriptive statistics, frequencies, percentages, and median values were calculated. Data were presented as median (min-max) or number and percentage of patients.

Results

Patient characteristics are listed in Table 1. In 34 of 442 patients (22 males and 12 females) who were retrospectively analyzed in the last 10 years, the thrombus was transcending the renal vein and extending to the IVC. Tumor thrombus extending to the IVC was classified as level I, II, and III in 20 (58.8%), 9 (26.4%), and 5 (14.7%) patients, respectively. No patient had level IV thrombus. At the time of diagnosis, 4 (11.7%) patients had flank pain and hematuria, 3 (11.7%) had weight loss, 1 (8.8%) had mild edema, and 1 (2.9%) had bilateral varicocele. Preoperative renal artery embolization was not performed in any of the patients who had surgical treatment. None of the patients needed cardiopulmonary bypass (CPB) during surgical intervention. The postoperative pathological outcomes, complications, and tumor stages are shown in Table 2. Mean blood loss and operation times were 744 mL (range, 110–3500 mL) and 280 min (range, 120–430 min), respectively. Ten patients (29.4%) with blood loss >1500 mL received blood transfusions. Pathological examinations and staging of renal tumor revealed that 25 (73.5%) patients had clear cell carcinoma, 5 (14.7%) had chromophobe carcinoma, 2 (5.8%) had sarcomatoid carcinoma, 2 (5.8%) had papillary carcinoma, and 6 (17.6%) had positive lymph nodes. The Fuhrman grades included 20.5% (n=7) grade 2, 44.1% (n=15) grade 3, and 20.5% (n=7) grade 4. There were no Fuhrman grades in the 5 patients with chromophobe carcinoma. There were no pathologically positive surgical margins in any case. In 2 patients, tumors were seen to be adherent to the caval wall requiring a bigger caval resection; caval venotomies were sutured using a bovine patch to maintain the luminal caliber of the vena cava. Patients were discharged with a mean hospitalization time of 10.6 days (range, 5–23 days). There were 9 (26.4%) cases with 10 complications, including 8 minor complications (Clavien grades 1–2). The remaining 2 complications (Clavien grades 3–5) were major of which one patient with level III thrombus died of pulmonary embolism on day 17 post operation; the other patient had an abscess at the site of surgery, which needed a percutaneous drainage. Twenty patients were transported to the intensive care unit after surgery for a hemodynamic follow-up until they were sufficiently stable to be transferred to our urology department. The mean follow-up period was 36 months (range, 6–72 months). Three (8.8%) patients showed distant metastasis during the postoperative

Table 1. Characteristics of the patients (n=34)

Parameters	Values
Gender, n (%)	
Male	22 (64.7)
Female	12 (35.3)
Median age, years (range)	61 (49–69)
Median tumor size, cm (range)	10.5 (7–18)
Tumor thrombus level, n (%)	
Level I	20 (58.8)
Level II	9 (26.4)
Level III	5 (14.7)
Tumor side, n (%)	
Right	21 (61.8)
Left	13 (38.2)
Symptoms, n (%)	
Hematuria	4 (11.7)
Weight loss	3 (8.8)
Flank pain	4 (11.7)
Bilateral varicocele	1 (2.9)
Swelling of the legs	1 (2.9)
Prior pulmonary embolism	0

Table 2. Postoperative complications, pathological findings, surgical features, and tumor stage

Parameters	Values
Postoperative complications, n (%)	
Minor complications (Clavien grades 1–2)	8 (23.5)
Major complications (Clavien grades 3–5)	2 (5.8)
Pathological features, n (%)	
Clear cell	25 (73.5)
Papillary	5 (14.7)
Chromophobe	2 (5.8)
Purely sarcomatoid	2 (5.8)
Stage, n (%)	
pT3b	32 (94.1)
pT3c	2 (5.8)
pN0	0
pN1	6 (17.6)
M0	0
M1	0
Nuclear grade, n (%)	
2	7 (20.5)
3	15 (44.1)
4	7 (20.5)
Microvascular invasion, n (%)	
Present	19 (55.9)
Absent	15 (44.1)
Margin status, n (%)	
Negative	32 (94.1)
Positive	1 (2.9)
Unknown	1 (2.9)
Cases of transfusion, n (%)	10 (29.4)
Estimated median blood loss, mL (range)	744 (110–3500)
Median operative time, min (range)	280 (120–430)

follow-up at a mean of 36 months (18, 42, and 48 months). In total, 30 patients were alive at 48 months, and 1 patient could not be reached at 6 months after the surgery. The progression-free survival rate at 36 months was 73.5%. The overall survival rate at 60 months was 85.2%.

Discussion

In adults, RCC comprises 3.5% of malignant neoplasms and is the most lethal, with a mortality rate of 40% among urological cancers.[1] Historically, up to 10% of patients with RCC have tumor thrombus involving the renal vein or vena cava and 1% have tumor thrombus extending into the right atrium.[2,3,11] Venous thrombus is often seen in the right kidney due to shortness of the right renal vein.

Patients with thrombus extending to the renal vein, IVC, or right atrium present a surgical treatment challenge. A multidisciplinary approach is of critical importance in the treatment of these patients because the presence of thrombus with the tumor can lead to complications, such as venous congestion and embolic events. RCC patients with tumor thrombus should be considered for a surgery on the IVC rather than on the kidney. Early radical operation is the most effective method in terms of survival because it is resistant to non-surgical treatment modalities, such as chemotherapy and radiotherapy.[11] In many studies, the 5-year survival rate after radical nephrectomy and thrombectomy were 35%–78%.[11-13] The 5-year survival rate in our study was found to be 85%. The reasons for this high rate were the lack of patients with level IV tumor thrombus and a team working in good harmony.

Survival in crucial in the absence of metastases or positive regional lymph nodes. Even in cases of distant metastasis, cytoreductive operations can significantly improve the quality of life and prolong survival.[14] However, extraction of caval thrombus together with renal tumor is technically difficult and associated with a major perioperative morbidity rate of up to 70% and a mortality rate of up to 48%.[14] Even if there are various prognostic variables, such as tumor size, histological subtype, grading, presence of sarcomatoid features, invasion of perirenal tissues, and nodal or distant metastasis as well as tumor thrombosis, very few factors specific to these patients are available and their role remains a controversial issue, as it is for the cranial level reached by the thrombus. The prognosis after surgery is comparatively better in patients with tumor limited to the kidney and without caval wall involvement. The correlation between the level of tumor thrombus in IVC and prognosis is now uncertain.[13] Many studies have reported no considerable difference in survival based on the extent of tumor thrombus. These findings are supported by Kim et al.[15] who noticed that the level of thrombus was not a predictor of cancer-specific survival on multivariate analysis In contrast, some authors have reported that tumor thrombus extending to the right atrium influences survival more adversely than subdiaphragmatic tumor thrombus.[16,17] In rare cases, tumor thrombus can invade into the caval wall and reconstruction of the vena cava may be necessary. IVC reconstruction can be performed using a patch or a graft. In the present study, 2 patients with an IVC diameter of more than 2.5 cm had caval wall invasion that required larger caval resection. Thereafter, resection venotomy was closed using a bovine patch.

The management of RCC with tumor thrombus frequently requires collaboration between different specialists, including

an anesthetist, urologist, cardiovascular, and occasionally transplant operators. Due to the increase in the cooperation between clinics, positive improvements in surgical techniques and postoperative care have led to a significant reduction in mortality and morbidity over the years. In this context, when the 30-year experience of Mayo Clinic with high patient volume was examined, the complication and operative mortality for 1970–1989 and 1990–2000 were reported as 13%–8% and 54%–2%, respectively.[17] Additionally, perioperative mortality rates were reported as 3% and 9.6% in cases with IVC thrombus in many other retrospective studies.[18,19] Only one (2.9%) patient who was operated in our clinic died on day 17 post operation. When compared to literature, the mortality rates in our study were lower because of careful preoperative planning, a precise and delicate surgical technique, multidisciplinary approach, and close follow-up peri/post operation.

The level of thrombus determines the surgical technique and states which could include total nephrectomy, limited or extensive IVC dissection, or CPB. Regardless of the tumor thrombus level, suspected invasion of the caval wall requires partial or total resection of IVC to achieve complete tumor resection. Tumor thrombus at high positions (e.g., thrombus invading into the right atrium) always requires complex surgical operations, such as CPB, cardiac arrest, or thrombus monitoring through transesophageal echocardiography, which can cause serious complications. CPB with hypothermia carries a known risk of perioperative bleeding due to platelet dysfunction and systemic heparinization. Other known risks of CPB are sepsis, multiorgan failure, longer operative times, postoperative bleeding, and neurological deficits.[19] In addition, specific, expensive equipment and highly trained personnel are required. Some authors argue that even if the thrombus reaches the right atrium, CPB should not be used.[20,21] Few authors have indicated that to reduce the intraoperative blood loss, to facilitate a direct route to the renal hilum, and to minimize the tumor thrombus, arterial embolization to the affected kidney can be done.[22] Performing surgery in a cardiovascular operating room has some benefits, such as facilitating toward CPB if needed and having a cardiovascular surgical team ready together with an anesthetic team familiar with cardiovascular procedures. We believe that working with a full team spirit will decrease the possible complications because it will increase the motivation. No patient had CPB or preoperative arterial embolization in our study. Apart from these techniques, we prefer controlling posterior venous branches and an early ligation of the renal artery to provide a better view, resect the thrombus completely, and reduce the amount of blood loss.

Patients with tumor thrombus in the IVC are usually symptomatic at the time of diagnosis and are diagnosed incidentally during radiological studies for other reasons.[5] The extent of the local tumor can cause symptoms that are commonly presented as hematuria or flank pain and other symptoms, such as weight loss, tiredness, or paraneoplastic syndrome. Lower extremity edema and new onset varicocele due to the mechanical occlusion of IVC or pulmonary embolism due to the migration of the thrombus can be seen. In our study, 26.4% (n=9) patients were symptomatic at the time of diagnosis, which was less compared to literature. We link this situation to the lack of patients with locally advanced tumor thrombus above the diaphragm. The main limitations of our study were its retrospective design in a single institution and the relatively small number of cases.

In conclusion, patients with RCC that invades the venous system require a challenging radical surgical approach in urological oncology. Patients with RCC and infra-diaphragmatic tumor thrombus can be treated safely and effectively through radical nephrectomy and total caval thrombectomy without using CPB. We think that radical surgical management of RCC extending to IVC requires the commitment of a multidisciplinary surgical team especially for a higher level tumor thrombus. Furthermore, we believe that working in harmony with other clinics reduces morbidity and mortality.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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