



Renal Cell Carcinoma with Level IV Cavo-Atrial Thrombus: Short Term and Long Term Outcomes

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Abstract

Introduction: With the technological advances surgical treatment of Renal Cell Carcinoma with a level IV Cavo-Atrial Thrombus is now feasible, and the thrombus can almost always be removed successfully. Patients with level IV Inferior Vena Caval thrombus can be treated safely and effectively via radical nephrectomy and thrombectomy using Cardiopulmonary Bypass combined with Deep Hypothermic Circulatory arrest.

Materials and Methods: During the study period, 20 patients (16 male and 4 female) underwent surgery for RCC with IVC tumor thrombus extending into the right atrium. Preoperative workup included chest, abdomen and pelvis CT scan, and Magnetic Resonance Imaging (MRI). Following surgery all of the patients were followed up with a complete blood serum chemistry panel, chest X-ray and abdominal CT.

Results: A total of 20 patients with mean (SD) age of 49.65 ± 10.32 years underwent radical nephrectomy with IVC thrombectomy. Preoperatively all these patients were diagnosed to have a T3cN0M0 RCC on clinical and radiological imaging. The mean (SD) operating time was 247.25 ± 40.08 mins, and the mean (SD) hypothermic circulatory arrest time was 17.25 ± 1.48 mins at a mean core temperature of $20.4 \pm 2.8^\circ\text{C}$. In a mean follow of 40.85 months, malignancy was the cause of death in 9 of these patients, whereas five other patients died of causes unrelated to RCC and six patients are still alive postoperatively. The median survival after the operation was 31.5 months.

Conclusion: Patients with level IV IVC thrombus RCC can be treated safely and effectively via radical nephrectomy and thrombectomy using CPB combined with DHCA. This approach is associated with low rates of morbidity and mortality.

Keywords: Cardiopulmonary bypass; Hypothermic arrest; Renal cell carcinoma; Thrombectomy; Tumor thrombus

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Introduction

Formation of tumor thrombus and venous migration are unique to Renal Cell Carcinoma (RCC) [1] with significant therapeutic and prognostic implications [2]. IVC (Inferior Vena Cava) thrombus occurs in 4% to 10% of patients with renal cell carcinoma [3] of which 2% to 16% are known to extend into the right atrium [4]. The tumor thrombus is known to invade the caval wall which is however difficult, if not impossible, to predict preoperatively [1]. The intravascular growth observed in RCC patients could signify a heightened or more aggressive biologic behaviour of the tumor. Several experts agree that the RCC associated tumor thrombus does not translate to a specific prognostic significance if it can be treated successfully with surgery [5]. Radical nephrectomy together with thrombectomy is the only effective therapeutic option for these patients [6,7]. Surgical management of RCC in which there is extension into the renal vein, IVC, or even the right atrium, however, poses a significant technical challenge [8].

Several contemporary studies have demonstrated that tumor thrombus has a limited prognostic role in the absence of nodal and/or metastatic disease and that about 45% to 70% of cases can be cured with surgical extirpation [2,9]. While others have shown that the prognosis of RCC with IVC thrombi is generally poor with 5 year survival rates about 25% to 57%, despite surgical resection of RCC and tumor thrombus [2,10]. Reported operative mortality rates range between 2.7% to 13% [11]. The major causes of death being pulmonary embolism and myocardial infarction or due to complications related to the bypass procedures. However, with better perioperative management and standardization of the surgical techniques, the mortality rates have decreased considerably [4]. In the present study, we have retrospectively reviewed our management of RCC cases with level IV

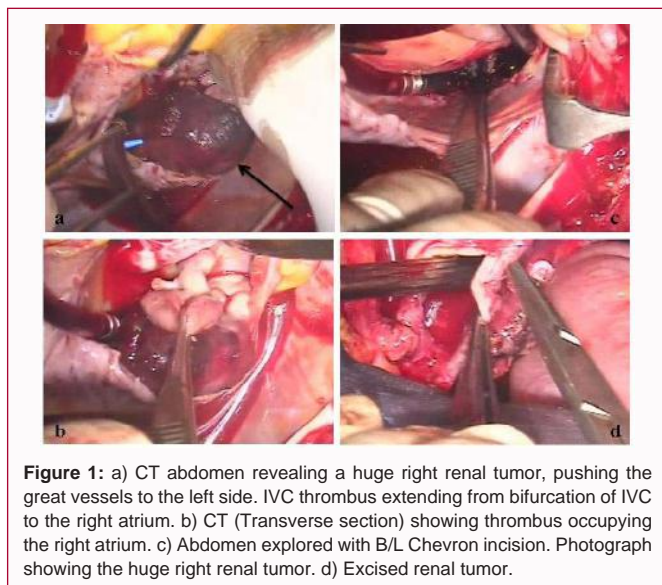


Figure 1: a) CT abdomen revealing a huge right renal tumor, pushing the great vessels to the left side. IVC thrombus extending from bifurcation of IVC to the right atrium. b) CT (Transverse section) showing thrombus occupying the right atrium. c) Abdomen explored with B/L Chevron incision. Photograph showing the huge right renal tumor. d) Excised renal tumor.

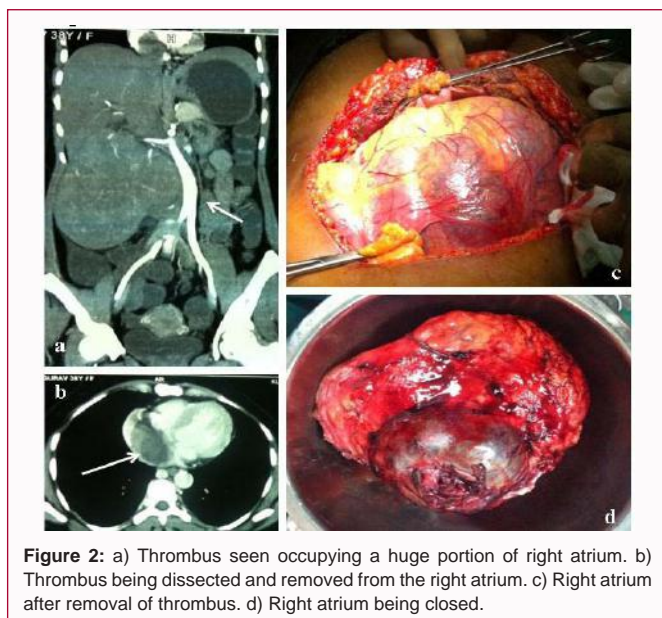


Figure 2: a) Thrombus seen occupying a huge portion of right atrium. b) Thrombus being dissected and removed from the right atrium. c) Right atrium after removal of thrombus. d) Right atrium being closed.

thrombi using the Cardiopulmonary bypass with deep hypothermic circulatory arrest approach. We have analysed our data to assess short and long term outcomes.

Patients and Methods

During the period Jan 1996 to Dec 2015, 20 patients (16 male and 4 female) underwent surgery for RCC with IVC tumor thrombus (level IV) extending into the right atrium. Preoperative workup included chest, abdomen and pelvis CT scan, abdominal ultrasound with color-Doppler, and Magnetic Resonance Imaging (MRI) (Figure 1). Magnetic resonance imaging was done to determine the exact cephalad extent of the inferior vena cava thrombus. Loco-regional and metastatic extension was evaluated in all cases by brain and chest CT-scan, bone scan and hepatic ultrasound.

Surgical techniques

Trans-Esophageal Echocardiography (TEE) was performed at the beginning of the surgical procedure in all patients to confirm the level of the upper extent of the thrombus. TEE was continued throughout the operation to detect air or tumor embolisms, and

to check complete extraction of the thrombus. The abdomen was entered through a bilateral chevron incision and extended through a median sternotomy. The right colon and small bowel were mobilized along the white line of Toldt and small bowel mesentery, exposing the anterior surface of the inferior vena cava and both the renal veins. The involved kidney was dissected from all the sides and the renal artery ligated. Infra-renal IVC and contralateral renal vein were clamped using a tourniquet. The patient was placed in the Trendelenberg position to decrease the risk of air embolism. The renal vein on the affected side was ligated and the nephrectomy was completed. Further the patient was heparinised and cannulation was performed. The right atrium was cannulated with minimal handling and avoiding the tumour thrombus. A low profile 'Ross basket' cannula was inserted into the right atrial appendage. Cardiopulmonary Bypass (CPB) was commenced and the patient was systematically cooled to a core temperature of 23°C to 25°C. After the required temperature was attained, the patient was placed in Trendelenberg position. A separate atriotomy was made almost to the level of the diaphragm to allow complete visualization (Figure 2). The intra-abdominal IVC was simultaneously opened. The thrombus was gently manipulated and separated from the IVC, hepatic veins and Right Atrium (RA). The 'tumour waist' at the level of the diaphragm required careful manipulation to deliver the tumour tissue into the abdominal IVC. Another area of concern was the hepatic veins, which contained 'tongues' of tumour tissue and required exploration under vision via the RA to extricate. This was further aided by the use of Fogarty's embolectomy catheter. The thrombectomy was completed. The cavotomy and atriotomy were then closed with continuous polypropylene sutures. Cardiopulmonary bypass was reversed, aortic clamp removed and the patient was rewarmed. All of the patients were followed up with a complete blood serum chemistry panel, chest X-ray and abdominal CT at 6 monthly intervals postoperatively. Bone scans were done whenever necessary. All hospital charts and follow-up information was obtained by contacting the patients and/or their attenders. Complete follow-up was available for all the patients. Cancer free status was determined by negative findings on the aforementioned studies. Survival analysis was calculated and the mean survival reflected the interval to last follow-up in patients still alive or to death.

Results

During the study period of eighteen years, 28 patients with RCC and level IV cavo-atrial thrombus presented to the uro-oncological services of the hospital. Of these a total of 20 patients with mean (SD) age of 49.65 ± 10.32 years underwent radical nephrectomy with IVC thrombectomy. Twelve had RCC on the right side and the remaining eight had on the left side. All these patients had a T3cN0M0 RCC on clinical and radiological imaging. Preoperative evaluation in these patients showed that, hepatic enzymes and serum bilirubin was raised in three patients, two other patients had raised serum creatinine levels and all the 20 patients were anemic. Minimal ascites was noted in three patients and prominent veins over abdomen were visible in 13 of the patients. Pre-operative blood transfusion was necessary in five patients. Following discussions with the cardiothoracic team, it was decided to perform the surgery using cardio-pulmonary bypass and instituted hypothermic circulatory arrest. All patients were started on heparin preoperatively. The mean (SD) operating time was 247.25 ± 40.08 mins, and the mean (SD) hypothermic circulatory arrest time was 17.25 ± 1.48 mins at a mean core temperature of 20.4 ± 2.8°C. Complete removal of the tumour thrombus was accomplished in all

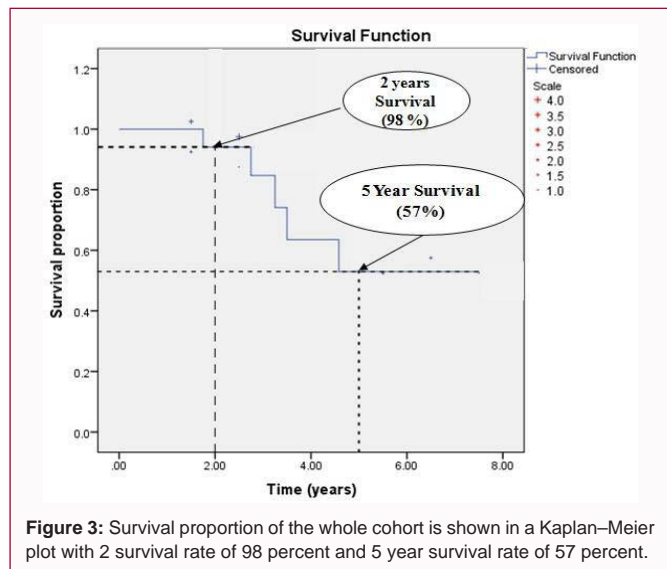


Figure 3: Survival proportion of the whole cohort is shown in a Kaplan–Meier plot with 2 survival rate of 98 percent and 5 year survival rate of 57 percent.

patients within the period of circulatory arrest. Post-operative blood loss was <650 ml in all but three patients.

The histological types were: clear cell RCC in 17 cases (Fuhrman nuclear grade II in two, grade III in fourteen, and grade IV in one), papillary RCC in two cases (Fuhrman nuclear grade III), and Primitive neuroectodermal tumor in one case. Perinephric fat involvement (T4) was seen in four patients and hilar lymph nodes (N1) were positive for tumor in five. None of the patients died during the period of hospitalization. Two patients were re-explored within 8 hours for post-operative bleeding. The bleeding was noticed from the pericardium in one and the internal mammary vessels in the other. Post-operative blood transfusions were necessary in three patients. The mean intensive care and hospital stay was 3.0 and 14.5 days respectively. Immediate postoperative complications were as shown in (Table 1). The raised preoperative hepatic parameters in three patients gradually returned to normal in the postoperative period. Serum creatinine which was raised in two patients preoperatively similarly showed decline, but not to normal levels. In a mean follow of 40.85 months (range 16 - 90), malignancy was the cause of death in 9 of these patients, whereas five other patients died of causes unrelated to RCC which included myocardial infarction (3), cerebrovascular accident (1) and road traffic accident (1). Six patients are still alive at 21, 33, 39, 42, 55 and 65 months postoperatively (median 40.5 and mean 42.5 months). The median survival after the operation was 31.5 months. Survival proportion of the whole cohort is shown in a Kaplan–Meier plot (Figure 3) with 2 survival rate of 98 percent and 5 year survival rate of 57 percent.

Discussion

Today radical surgery remains the mainstay of curative treatment for RCC (Renal Cell Carcinoma). Progression of a tumour thrombus into the inferior vena cava (IVC) makes surgery all the more challenging. Clinically, four levels of thrombus extension into the IVC have been defined by Nesbitt et al. [4]. In level IV, the thrombus extends above the diaphragm into the right atrium, and the operating uro-oncological team would need the help of the cardiothoracic surgeons. Due to the scarcity of these operations, usually only case reports or small series with short follow-up have been published to date. Venous involvement was once thought to be a very poor prognostic finding for RCC, but several reports demonstrate that

Table 1: Immediate Postoperative complications.

No	Complications		Outcome
1	Bleeding	2	Re-exploration and control
2	Poor Respiratory attempts /Infection	1	Prolonged ventilation
3	Wound infection	3	Wound dressing

many patients with tumor thrombi can be salvaged with an aggressive surgical approach. These studies document 45% to 69% 5-year survival rates for patients with venous tumor thrombi as long as the tumor is otherwise confined to the kidney [12,13]. Patients with venous tumor thrombi and concomitant lymph node or systemic metastases have markedly decreased survival, and those with tumor extending into the perinephric fat have intermediate survival [13,14]. The prognostic significance of the cephalad extent of tumor thrombus appears to be controversial, and it is difficult to compare various series because of selection biases and related co-variables [14]. In several series the incidence of advanced loco regional or systemic disease increased with the cephalad extent of the tumor thrombus, accounting for the reduced survival associated with tumor thrombus extending into or above the level of the hepatic veins [14,15]. However, other data suggest that the cephalad extent of tumor thrombus is not of prognostic significance as long as the tumor is otherwise confined [13]. Direct invasion of the wall of the vein appears to be a more important prognostic factor than level of tumor thrombus and is now classified as pT3c independent of the level of tumor thrombus [13-16]. Involvement of the IVC with RCC renders the task of complete surgical excision more complicated; however this approach offers the only realistic hope for cure for most patients. Vascular control for level III and level IV IVC thrombi requires more extensive dissection, venovenous bypass, or cardiopulmonary bypass and hypothermic circulatory arrest. Level IV IVC thrombi have traditionally been managed with Cardiopulmonary Bypass (CPB) and Hypothermic Circulatory Arrest (HCA), and this is still the preferred approach in complex cases [13-15]. Several centers are now trying to avoid hypothermic circulatory arrest and the associated hypocoagulable state that ensues after coming off the pump and the increased risk of cerebrovascular accident and myocardial infarction that accompanies this procedure [7,13]. In this case the thrombus is mobilized below the atrium, allowing sequential vascular control to be achieved without opening the heart.

Chen, et al. [17] performed a retrospective analysis on 32 RCC patients with IVC thrombus that underwent nephrectomy and thrombectomy via the minimally invasive CPB/HCA approach. The median operation time was 360 min (Inter Quartile Range (IQR): 300 to 435 min) with median CPB and HCA durations of 149 min and 23 min, respectively. The median estimated blood loss was 2,500 ml. Four complications were observed but no deaths occurred peri-operatively. The median follow-up was 25 months (range: 4 to 64 months). The mean Overall Survival (OS) was 28.2 ± 4.6 months while the Disease-Free Survival (DFS) was 19.5 ± 11.6 months. In patients with M0 disease, ten patients developed metastases and were treated with sorafenib as an adjuvant therapy. The mean OS and DFS of this subgroup were 25.4 ± 12.8 months and 16.0 ± 14.2 months, respectively. Dominik et al. [18]. evaluated long-term results of surgical management of renal cell carcinoma with level IV tumour thrombus in a large single institution series. Radical nephrectomy was performed followed by sternotomy, institution of cardiopulmonary bypass and extraction of the intracardiac tumour thrombus under direct visual control during Deep Hypothermic Circulatory Arrest

(DHCA). The mean (SD) duration of circulatory arrest was 16 ± 6 min at a mean hypothermia of $20 \pm 3^\circ\text{C}$. In-hospital mortality was 9.5%. The median survival (including in-hospital mortality) was 25 months. In Kaplan-Meier analysis, 2 and 5-year overall cumulative survival rate was 57 (95% confidence interval, CI 36–78) % and 37 (95% CI 15–58) %, respectively. Cancer-specific cumulative survival was 68 (95% CI 49–89)% at 2 years and 51 (95% CI 28–74) % at 5 years. Similarly Nerli et al. [15]. Assessed the short term and long term survival of 7 patients with level IV thrombus who underwent surgical treatment for localized RCC and inferior vena caval thrombus extending into the right atrium using Cardiopulmonary Bypass (CPB) and deep hypothermic circulatory arrest. Pathological investigations revealed no renal capsular penetration of RCC in 4 patients and perinephric fat involvement in 3. The mean operating time was 365 min (295–390), anesthesia time was 395 min (335–440), cardiopulmonary bypass time was 128 min (38–200) and hypothermic circulatory arrest time was 28 min (14–38). The mean follow-up time was 38 months. Presence of capsular infiltration or positive lymph nodes significantly affected survival of patients, with no patient having a two year survival as opposed to 100% in patients with no capsular infiltration. The authors concluded that long term survival following the surgical treatment was possible in individuals with localized RCC extending into the right atrium. Performance of complete radical nephrectomy along with vena caval thrombectomy under circulatory arrest was safe and without significant morbidity. Chowdhury et al. [19]. Described an alternative technique of vena caval and intra-arterial tumor thrombectomy to decrease perioperative mortality and morbidity. Radical nephrectomy with tumor thrombectomy from the vena cava and right atrium was performed under mild hypothermic cardiopulmonary bypass and intermittent cross-clamping of the supraceliac abdominal aorta. Interatrial tumor thrombectomy was performed on a beating, perfused heart in 4 patients and a hypothermic, cardioplegia-perfused heart in 2 patients. The aortic cross-clamp time was 12 and 15 minutes for two patients respectively. The cumulative hepatic and renal ischemic time was 16 minutes (range, 14 to 22 minutes) at 32°C . The mean cardiopulmonary bypass time was 53.3 ± 8.9 minutes (range, 40 to 65 minutes). At a mean follow-up of 43 ± 24.6 months (range, 10 to 70 months), all patients were active and remained disease-free. Modine et al. [20]. Reported on their early experience with a simplified CPB technique, wherein the right atrium thrombus was extracted under normothermic CPB without cross clamping or cardioplegic arrest. A cavotomy was performed at the ostium of the renal vein and an endoluminal occlusion catheter was introduced to perform the thrombectomy. Atrial and caval thrombectomy were achieved successfully. Currently, better surgical results than those published can be expected because of the enormous improvement in perioperative and postoperative care. A risk of 5–10% can currently be hypothesized for an operation with the use of DHCA in patients with RCC/level IV cavo-atrial thrombus [18]. Long-term results are of equal importance and also justify the correctness of such a complex and demanding surgical procedure needed to treat these level IV IVC thrombus. In a retrospective study including 1192 patients operated for RCC with tumour thrombus between 1982 and 2003 at 13 European institutions [21], the median survival was only 18 months for 63 patients with supra-diaphragmatic tumour thrombus. Independent prognostic factors in multivariate analysis were tumour size, perinephric fat invasion, lymph node invasion, tumour thrombus level and distant metastasis [21]. There was no improvement in postoperative survival of patients with multiple distant metastases when compared with the

natural history of untreated RCC [22]. In another multi-institutional study that collected retrospective data from 11 USA and European academic institutions between 1970 and 2006 [23], 77 patients had tumour thrombus extending into the right atrium; with median survival time of 12 months and 22% 5-year cumulative survival. In a multivariate analysis, tumour size, Fuhrman grade, nodal metastasis and tumour thrombus level correlated independently with the survival. Mohammed Nouh et al. [24] has made a suggestion about angioscopic removal of such tumor thrombi under direct vision. Such an endoscopic removal of the tumor thrombi could provide several advantages. At first, it would allow direct visualization of the tumor thrombi and the caval lumen throughout the technique. Secondly, it would avoid the aggressive time-consuming dissection of IVC from the posterior abdominal wall and liver mobilization with their surgical consequences. Thirdly, it would allow removal of thrombi in a relatively bloodless field. Fourth, it would reduce the length of incision and soft-tissue dissection. Fifth, it would avoid the complicated techniques and the surgical consequences of CPB and DHCA.

Conclusion

Patients with level IV IVC thrombus RCC can be treated safely and effectively via radical nephrectomy and thrombectomy using CPB combined with DHCA. This approach is associated with low rates of morbidity and mortality.

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