

Cardiopulmonary Bypass has No Significant Impact on Survival in Patients Undergoing Nephrectomy and Level III-IV Inferior Vena Cava Thrombectomy: Multi-Institutional Analysis

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Abbreviations and Acronyms

CPB = cardiopulmonary bypass
CSS = cancer specific survival
LOS = length of stay
OS = overall survival
RCC = renal cell cancer

Accepted for publication February 10, 2015.
Study received institutional review board approval.

* Equal study contribution.

† Financial interest and/or other relationship with Cepheid, Wolf, Olympus, Ipsen, Astellas and Janssen.

‡ Financial interest and/or other relationship with MDx Health.

§ Financial interest and/or other relationship with Opko Pharmaceutical.

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Purpose: The impact of cardiopulmonary bypass in level III-IV tumor thrombectomy on surgical and oncologic outcomes is unknown. We determine the impact of cardiopulmonary bypass on overall and cancer specific survival, as well as surgical complication rates and immediate outcomes in patients undergoing nephrectomy and level III-IV tumor thrombectomy with or without cardiopulmonary bypass.

Materials and Methods: We retrospectively analyzed 362 patients with renal cell cancer and with level III or IV tumor thrombus from 1992 to 2012 at 22 U.S. and European centers. Cox proportional hazards models were used to compare overall and cancer specific survival between patients with and without cardiopulmonary bypass. Perioperative mortality and complication rates were assessed using logistic regression analyses.

Results: Median overall survival was 24.6 months in noncardiopulmonary bypass cases and 26.6 months in cardiopulmonary bypass cases. Overall survival and cancer specific survival did not differ significantly in both groups on univariate analysis or when adjusting for known risk factors. On multivariate analysis no significant differences were seen in hospital length of stay, Clavien 1-4 complication rate, intraoperative or 30-day mortality and cancer specific survival. Limitations include the retrospective nature of the study.

Conclusions: In our multi-institutional analysis the use of cardiopulmonary bypass did not significantly impact cancer specific survival or overall survival in patients undergoing nephrectomy and level III or IV tumor thrombectomy. Neither approach was independently associated with increased mortality on multivariate analysis. Greater surgical complications were not independently associated with the use of cardiopulmonary bypass.

Key Words: carcinoma, renal cell; cardiopulmonary bypass; vena cava, inferior; survival; intraoperative complications

RENAL cell carcinoma is the third most common genitourinary malignancy, accounting for 65,000 new cases and causing 13,600 deaths each year in the U.S.¹ Approximately 10% of the cases presented with tumor and/or thrombus involvement of the renal vein and vena cava. Of the patients with RCC 1% presented with tumor thrombus above the level of the hepatic vein (level III and IV).¹ Without treatment, patients with caval thrombus have a high mortality risk.² With aggressive surgical treatment 5-year CSS reaches 50% in nonmetastatic cases and OS approaches 40%.^{3,4}

Surgical treatment of level III/IV thrombi is associated with high perioperative mortality and morbidity. These cases often require the use of CPB with or without hypothermia circulatory arrest. Previous studies have reported on the success of performing level III/IV thrombectomy without the use of cardiopulmonary bypass, given the associated morbidity when placing patients on CPB.¹ Most surgeons advocate for the use of CPB in complex cases involving tumor thrombus extending into the right atrium.⁵ There is inconclusive evidence whether the use of CPB has any impact on short-term outcomes including intraoperative mortality, 30-day mortality, LOS and immediate surgical complications. The impact of CPB on cancer specific mortality and overall mortality is also unclear.

To address these shortcomings we analyzed the impact of CPB on long-term oncologic outcomes and immediate surgical outcomes in patients undergoing radical nephrectomy with level III/IV thrombectomy. We used a multi-institutional database from 22 U.S. and European centers to report the largest series to date to our knowledge.

PATIENTS AND METHODS

Patient Selection and Data Collection

This study was approved by the institutional review boards of all participating sites that provided the necessary institutional data sharing agreements before initiation of the study. We retrospectively analyzed 362 patients with RCC and with level III or IV tumor thrombus who underwent radical nephrectomy and complete tumor thrombectomy from 1992 to 2012 at 22 U.S. and European centers. The data were centralized via the IRCC-VTC (International Renal Cell Carcinoma-Venous Thrombus Consortium) to ensure data integrity and to address all data inconsistencies before the analysis as previously described.⁶ Detailed surgical data, demographics and pathological evaluation were available. Patients with incomplete records were excluded from the analysis.

Pathological Evaluation and Tumor Thrombus Levels

Pathological staging was determined using the 2009 TNM classification. For patients who had surgery before 2009,

pathological staging was reclassified using the 2009 TNM staging.⁷ Tumor thrombus levels were confirmed on preoperative magnetic resonance imaging or transesophageal echocardiography. The level of the thrombus was classified using the Mayo classification system.⁸ Level III thrombus involves the intrahepatic inferior vena cava but below the diaphragm and level IV tumor thrombus extends above the diaphragm or into the right atrium. Surgery times were determined using start of incision to completion of incision. Surgical complications were within 30 days and classified using the 2004 Clavien-Dindo grading system. Low grade and high grade complications were further stratified using Clavien 1-2 and Clavien 3-4, respectively.

Management and Followup

Management included neoadjuvant targeted therapy, adjuvant immunotherapy and targeted therapy, and was administered at the investigator's discretion to patients with metastatic disease. Preoperative angioembolization and lymphadenectomy were also performed at surgeon discretion and did not follow a predetermined protocol. Followup was performed at least every 3 months for the first year, semiannually for the second year and annually thereafter. Each visit included a physical examination, complete chemistry, hematology panels and diagnostic imaging (eg ultrasonography, chest radiography, computerized tomography of the abdomen/pelvis with intravenous contrast) at the discretion of the treating physician when clinically indicated.⁶ Cause of death was determined by the treating physicians by chart review corroborated by death certificates. The Martin criteria were used to qualify surgical complications and the Clavien-Dindo grading systems were used to classify complications.^{9,10}

Statistical Analysis

Cox proportional hazards models were used to compare overall and cancer specific survival between patients with and without cardiopulmonary bypass. Median survival was estimated using the Kaplan-Meier method (log rank test). The effects of CPB on LOS were analyzed using quasi-Poisson models, which model count data while allowing for overdispersion. The effects of CPB on the odds of complications, intraoperative mortality and 30-day mortality were analyzed using logistic regression. Analyses were conducted using R, version 2.15.1 (R Core Team, 2012) and version 3.1.0 (R Core Team, 2014, intraoperative mortality, 30-day mortality, and low and high grade complication analyses only) as described previously.¹¹

RESULTS

Patient Characteristics

Median followup was 14.9 months in nonCPB cases (227) and 12.7 months in CPB cases (135). Supplementary table 1 shows patient characteristics dichotomized into with vs without the use of CPB (<http://jurology.com/>). Mean age was 63 years in both groups. Patients with CPB tended to have a longer surgery duration, were more likely to have a

level IV thrombus and had a lower incidence of synchronous metastatic disease at presentation. As shown in table 1 the overall complication rate was 53% in patients who underwent level III/IV thrombectomy, the nonCPB cohort had a high grade (major) complication (Clavien 3-4) rate of 28% while the CPB cohort had a high grade complication rate of 23%. Intraoperative mortality for patients with or without CPB was 2.2%. The 30-day mortality for nonCPB cases was 7.5% vs 10% for CPB cases.

Surgical Outcomes

On univariate analysis LOS was estimated to be 18% higher in CPB cases ($p = 0.042$), but when adjusting for other factors on multivariate analysis no significant difference was seen in LOS ($p = 0.667$). When looking at overall complications (Clavien 1-4) there was no significant difference in the odds of complication after adjusting for thrombus level, clinical and pathological characteristics, presence of metastasis and time under surgery.

We further classified complications into low grade (Clavien 1-2) and high grade (Clavien 3-4), and analyzed their association with the use of CPB. The rates of high grade or low grade complications were not significantly associated with surgical approach when adjusted for thrombus level, time of surgery and other factors. In addition, when analyzing level III and level IV thrombus separately, the complication rate was not significantly associated with the use of CPB (supplementary table 2, <http://jurology.com/>).

Next we proceeded to determine if the role of CPB had any association with increased risk of intraoperative mortality and 30-day mortality. On univariate analysis there was no significant association between CPB and intraoperative mortality ($p = 0.995$). There were 8 intraoperative mortalities, which was not enough to fit multivariable

Table 1. Patient outcomes

	No CPB	CPB	All Level III + IV	p Value*
No. complications (%):				0.011
No	34 (40)	21 (67.7)	55 (47.4)	
Yes:	51 (60)	10 (32.3)	61 (52.6)	
High grade	24 (28.2)	7 (22.6)	31 (26.7)	
Low grade	27 (31.8)	3 (9.7)	30 (25.9)	
No. intraop mortality (%):				>0.999
No	219 (97.8)	132 (97.8)	351 (97.8)	
Yes	5 (2.2)	3 (2.2)	8 (2.2)	
No. 30-day mortality (%):				0.431
No	198 (92.5)	118 (90.1)	316 (91.6)	
Yes	16 (7.5)	13 (9.9)	29 (8.4)	
Median mos followup (range)	14.9 (0–204)	12.7 (0–145)	14.2 (0–204)	0.535

* Fisher's exact test for categorical variables, from t-test for age, and from the t-test conducted on log-transformed data for followup duration and time in surgery.

models. Similarly, no significant association was seen between CPB and 30-day mortality on univariate analysis or multivariable analysis. Separate analysis of level III and level IV thrombus did not show any significant effect on perioperative mortality between CPB and nonCPB cases. In the level III thrombus cohort longer surgery time was associated with increased risk of 30-day mortality after adjusting for other variables (supplementary table 3, <http://jurology.com/>).

The use of CPB in patients with level III thrombus was associated with lower requirement of blood transfusion (supplementary table 4, <http://jurology.com/>). Liver mobilization was used 40% to 55% of the time regardless of whether patients were placed on bypass and did not appear to affect surgical outcome.

Long-Term Oncologic Outcomes

Median CSS was 34.0 months (95% CI 23.6, 64.7) in nonCPB cases and 39.7 months in CPB cases (95% CI 31.9, 80.0), with 151 cancer related deaths in the 2 groups. Figure 1 shows a Kaplan-Meier plot of CSS by CPB. (Note that the survival curves separate at the median but are nearly superimposed elsewhere.) CSS did not differ significantly based on CPB, neither on univariate analysis (Wald test $p = 0.942$) nor when adjusting for thrombus level, age, gender, T stage, N stage, presence of metastasis, time under surgery and time period of surgery (Wald test $p = 0.097$). Positive lymph node disease and metastasis were associated with CSS and OS on multivariate analysis (table 2).

Median OS was 24.6 months (95% CI 18.6, 34.5) in nonCPB cases and 29.3 months in CPB cases (95% CI 12.7, 35.7), with 211 deaths in the 2 groups. A total of 93 patients were still alive as of last

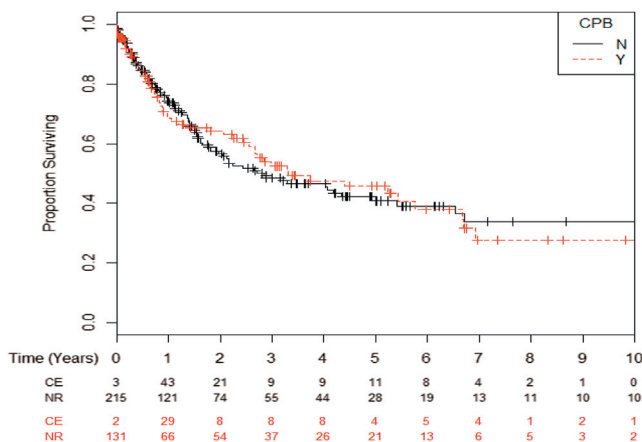


Figure 1. Kaplan-Meier plot of CSS by CPB, $p = 0.942$ (univariate).

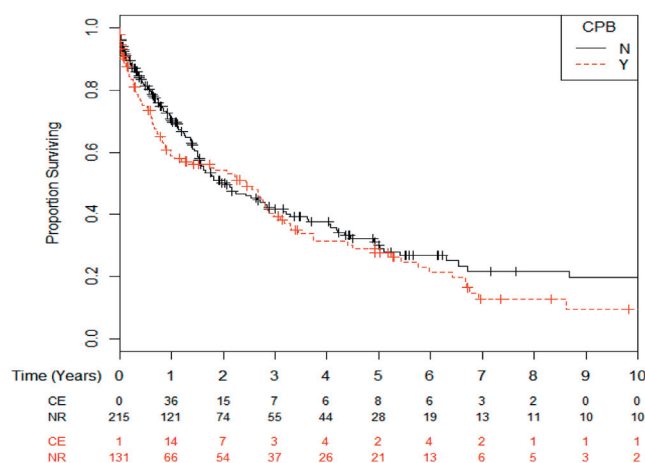
Table 2. Multivariable Cox proportional hazards model

	HR	95% CI for HR	p Value (Wald Test)
<i>Ca specific survival</i>			
CPB (yes vs no)	1.573	(0.921, 2.686)	0.097
Level (IV vs III)	1.131	(0.741, 1.725)	0.569
Age	0.998	(0.980, 1.018)	0.870
Gender (M vs F)	0.745	(0.498, 1.115)	0.1526
T stage (4 vs 3)	1.934	(0.903, 4.143)	0.089
N stage (N1 vs N0)	2.730	(1.503, 4.957)	0.001
N stage (N2 or N3 vs N0)	2.477	(1.362, 4.506)	0.003
N stage (NX vs N0)	1.138	(0.648, 1.999)	0.653
Hrs in surgery	1.057	(0.970, 1.151)	0.206
Metastases (M1 vs M0)	2.553	(1.470, 4.434)	0.001
Metastases (MX vs M0)	1.686	(0.968, 2.936)	0.065
<i>Overall survival</i>			
CPB (yes vs no)	1.544	(0.981, 2.430)	0.060
Level (IV vs III)	1.055	(0.737, 1.510)	0.769
Age	1.009	(0.992, 1.025)	0.322
Gender (M vs F)	0.935	(0.660, 1.323)	0.702
T stage (4 vs 3)	1.968	(1.002, 3.865)	0.049
N stage (N1 vs N0)	2.237	(1.324, 3.782)	0.003
N stage (N2 or N3 vs N0)	2.045	(1.189, 3.518)	0.010
N stage (NX vs N0)	1.357	(0.853, 2.158)	0.198
Hrs in surgery	1.054	(0.979, 1.136)	0.164
Metastases (M1 vs M0)	1.889	(1.184, 3.014)	0.008
Metastases (MX vs M0)	1.206	(0.763, 1.906)	0.422

followup. Figure 2 shows a Kaplan-Meier plot of OS by CPB. OS did not differ significantly based on CPB on univariate analysis or when adjusting for thrombus level, age, gender, T stage, N stage, presence of metastasis, time under surgery and time period of surgery. In a separate analysis in which we segregated patients into level III and level IV thrombus, there was no statistically significant impact of CPB on CSS or OS (supplementary figures 1 and 2, <http://jurology.com/>).

DISCUSSION

In patients undergoing level III/IV caval thrombectomy, the use of CPB allows the team of urologists

**Figure 2.** Kaplan-Meier plot of OS by CPB, $p = 0.235$ (univariate)

and cardiac surgeons to meticulously remove the tumor while having complete control over a bloodless field. When the tumor thrombus extends above the diaphragm, most surgeons are inclined to use CPB to allow maximal safety and oncologic control in case of unpredictable difficulty during the thrombectomy. However, there are also associated hematological and neurological morbidities when placing patients on CPB with or without circulatory arrest. Two single center series reported on the success of complete supradiaphragmatic tumor thrombus extraction without median sternotomy and CPB in 47 patients, with a 30-day mortality of 9.2% to 15% and a 19.5% incidence of high grade complications.^{5,12} Patil et al reported a median survival of 2.5 years for patients with pT3cN0 disease without the use of CPB.⁵

There are limited data on immediate surgical complications associated with the use of CPB in these patients, and most were reported from single center series, with the exception of 1 article that came from a 13-center analysis.^{1,13-18} These series reported complication rate ranges from 18% to 47% and perioperative mortality ranges from 7% to 22% in patients with level III/IV thrombus. In the present study we report oncologic and surgical outcomes in the largest cohort in the literature to our knowledge with level III/IV thrombus using the IRCC-VTC. As previously reported, patients with level III/IV thrombus often have significant complications associated with surgery, as high as 34% in the recent multicenter series using data from 162 patients.¹³ In our analysis 27% of the patients experienced high grade complications. When we controlled for thrombus level, time period of surgery and other covariates, the use of CPB did not have any impact on LOS and low or high grade complications.

Granberg et al reported a comparison of venovenous bypass vs cardiopulmonary bypass in 41 patients with level II-IV thrombus (venovenous bypass 13, CPB 28) and did not find a significant difference in complication rate or in 5-year cancer specific mortality with either approach.¹⁶ Similarly, we demonstrated that the use of CPB did not have any significant impact on short and long-term outcomes compared to nonCPB counterparts. In our cohort of 362 patients with level III/IV thrombus intraoperative and 30-day mortality was 2.2% and 8.4%, respectively, which is comparable to recently reported multicenter series.¹³ CPB and nonCPB were associated with 2.2% intraoperative mortality. Neither intraoperative mortality nor 30-day mortality was associated with or without the use of CPB in the combined (level III and IV) or separated analysis (level III or IV alone). Patil et al reported 3.4% intraoperative mortality

in their series of 87 patients with level III/IV tumor thrombus who underwent surgery without the use of CPB,⁵ while there is no report directly comparing CPB vs nonCPB with respect to intraoperative mortality.

In our long-term analysis of CSS and OS we did not find any significant impact on these oncologic outcomes associated with/without CPB on multivariate analysis. Our findings suggest that the decision regarding the use of CPB during level III/IV thrombectomy should be made on the basis of surgeon experience, perioperative imaging, patient comorbidities and the availability of a multispecialty team to maximize safety and cancer control. Limitations of our data were the retrospective nature of data collection, missing data, and the analyses being subjected to confounding variable and selection bias for which we could not control. However, this study offers insightful outcomes data based on a large international experience and may help guide decisions in surgical approach.

CONCLUSIONS

In the analysis of the largest cohort of patients with RCC tumor thrombus, the use of cardiopulmonary bypass did not significantly impact CSS or OS in patients undergoing nephrectomy and level III or IV tumor thrombectomy. Surgical complications (Clavien 1-4), intraoperative and 30-day mortality,

and hospital LOS were not independently associated with surgical approach (nonCPB vs CPB).

APPENDIX

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EDITORIAL COMMENT

The surgical management of renal cell carcinoma with associated venous tumor thrombus remains one of the most challenging yet rewarding operations in urology. Along with post-chemotherapy retroperitoneal lymphadenectomy, it is one of the few scenarios in which surgery for an advanced tumor has a significant oncologic benefit. When successful, patients may benefit from substantially increased longevity¹ and improved quality of life (eg pain, hematuria, lower extremity edema).

This report summarizes the large, multi-institutional experience with nephrectomy and associated tumor thrombectomy at or above the retrohepatic inferior vena cava and the impact of cardiopulmonary bypass. Of the patients in the series 37% underwent CPB, and the use of CPB was associated with level IV thrombus, more advanced disease and longer operative times. Nevertheless, there were no apparent differences in perioperative mortality or cancer specific survival, and median survival in both groups exceeded 24 months. Considering that nonsurgical management is associated with a median survival of 5 months (reference 2 in article), and the timing and role of systemic targeted therapy remain to be defined, the excellent outcomes reported in this study reinforce the role of surgery.

Despite advances in technology, the operative aspects of caval thrombectomy remain essentially unchanged with a variety of approaches and options. These likely depend as much on surgeon preference as on tumor and patient characteristics, and no single

technique is adequate. In addition, the urologist may require a multidisciplinary team including liver/transplant and cardiac surgeons.² Often complete mobilization of the liver permits not only access to tumors just above the diaphragm, but also control of the intrapericardial inferior vena cava and cavoatrial junction via incision of the diaphragm.

Much of the selection of surgical approach and need for CPB rely on surgeon experience and judgment, and the reported outcomes are from high volume centers. With CPB there are significant differences between hypothermia with circulatory arrest and “partial” bypass as well as methods of venovenous bypass. Some use the former for all atrial thrombi while others try to avoid sternotomy/CPB if at all possible, particularly for level III tumors. Although circulatory arrest provides the most control in a bloodless field, longer times are associated with risks of end organ injury and selective use of antegrade cerebral perfusion may mitigate some of the neurological effects.

The take home message is that these tumors can be managed by numerous surgical approaches tailored to patient, tumor and surgeon/center factors. Hopefully future studies will further guide decision making, and help reduce morbidity and mortality in these complex cases.

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