Original Article

Radiologic indicators prior to renal cell cancer thrombectomy: Implications for vascular reconstruction and mortality

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Abstract

Background: Renal cancer may invade the inferior vena cava (IVC) creating more complex surgical intervention. We investigate radiologic findings that may predict vascular reconstruction prior to surgery and future renal cancer-specific mortality.

Materials and Methods: Radiologic findings included Mayo Clinic risk factors for vascular reconstruction: Right-sided tumor, anteroposterior diameter of the IVC at the ostium of the renal vein ≥24.0 mm, and radiologic identification of complete occlusion of the IVC. Additional factors included thrombus in the lumen of the hepatic veins and metastasis. Along with other demographic factors, analysis included Chi-squared analysis for vascular reconstruction and logistic regression for mortality. A Kaplan–Meier curve was created for the most significant radiologic factor.

Results: Thirty-seven patients underwent IVC tumor thrombectomy at two institutions from April 2007 to February 2015. We found that Mayo risk factors of 0, 1, 2, and 3 and the proportions of vascular reconstruction of 0%, 0%, 12.5%, and 13.6%, respectively ($P = 0.788$). Hepatic vein involvement was the most significant determinate of renal cell carcinoma-specific mortality in multivariable analysis, controlling for the size of IVC at the hepatic veins, pulmonary metastasis, and Fuhrman grade ($P = 0.02$, Log-rank $P = 0.002$).

Conclusion: Mayo risk factors did not predict vascular reconstruction in our small cohort of Level II–Level IV IVC thrombus undergoing IVC thrombectomy. Tumor thrombus traveling into the lumen of the hepatic veins was a significant risk factor for accelerated mortality.

Key Words: Inferior vena cava thrombectomy, radiographic predictors of mortality, renal cell carcinoma

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INTRODUCTION

Renal cell carcinoma (RCC) has a tendency to extend into the venous system. A tumor thrombus extends into the inferior vena cava (IVC) in 4–10% of renal cancer cases.[1,2] The reported 5 years overall survival of these patients ranges from 32% to 69% without significance relative to the extent of the tumor

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thrombus.[3-6] Despite advances in cancer treatment, surgical resection has remained the standard treatment modality for this specific condition.[7,8]

Our group has employed a multidisciplinary approach to the retrohepatic and supradiaphragmatic IVC thrombectomy. Figure 1 demonstrates our standard for surgical exposure in these complex cases.

Accurate preoperative imaging has become imperative in evaluating the extent of disease as well as surgical planning.[9-11] The Mayo group recently evaluated and internally validated the use of several radiologic features that correlate with the need for IVC reconstruction at the time of resection.[12] However, no other known radiological factors are known to contribute to mortality besides overt metastasis. Figure 2 is a coronal computed tomography (CT) scan image of the retrohepatic IVC thrombus from the same patient in Figure 1.

Herein, we investigate a retrospective cohort of renal cell cancer patients undergoing tumor thrombectomy to attempt to externally validate the Mayo Clinic risk factors for prediction of vascular reconstruction compared to primary closure. Second, we utilize the established Mayo Clinic radiographic risk factors with other radiologic findings to determine important findings that may translate to RCC mortality.

MATERIALS AND METHODS

Patent population

The institutional review board approval was formally sought and officially obtained at all institutions prior to the initiation of the study. We then retrospectively reviewed all available data on consecutive patients who were diagnosed with RCC with suspicion of IVC involvement confirmed with imaging from April 2007 to February 2015. Patient cohorts from the University of Texas Health Science Center San Antonio and the University of California San Diego were combined and analyzed. Over this 8-year period, 37 total patients were identified to undergo formal chart review. The data constitutes a multi-surgeon cohort. No qualifying patients were excluded from the cohort at either site. Preoperative, intraoperative, and postoperative information were gathered on all 37 patients, which include preoperative IVC assessment and measurements, staging, intraoperative details, and follow-up length.

Outcomes and definitions

The primary outcome for this study was the need for IVC reconstruction at the time of surgery. The secondary outcome was RCC-specific mortality.

The classification system for venous invasion with tumor thrombus in RCC includes:

- Level I: Thrombus confined to renal vein
- Level II: Thrombus that extends within the IVC >2 cm above the confluence of the renal vein below the hepatic veins
- Level III: Thrombus that involves the intrahepatic IVC
- IIIa: Thrombus extending into the retrohepatic IVC but below the ostia of major hepatic veins
- IIIb: Thrombus extending into the retrohepatic IVC reaching the ostia of the major hepatic veins and may extend into them causing Budd–Chiari syndrome
- IIIc: Thrombus extending into the retrohepatic IVC above the major hepatic veins but below the diaphragm
- IIId: Thrombus extending into the supradiaphragmatic, intrapericardial IVC but not into right atrium
- Level IV: Thrombus that extends above the diaphragm or into the right atrium.[13,14]

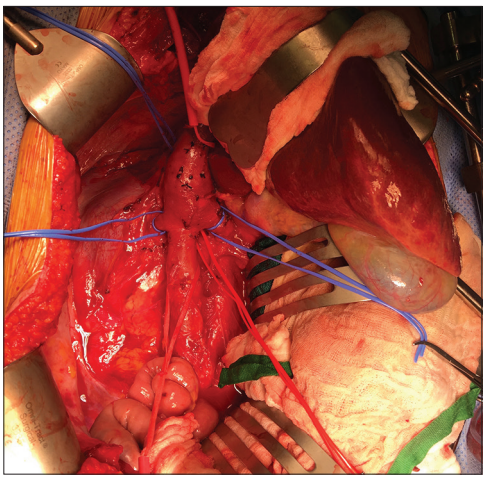

Figure 1: Intraoperative photo taken in October 2015 at the University Hospital in San Antonio, TX, demonstrating a complete vascular control of the inferior vena cava for an intrahepatic inferior vena cava thrombus

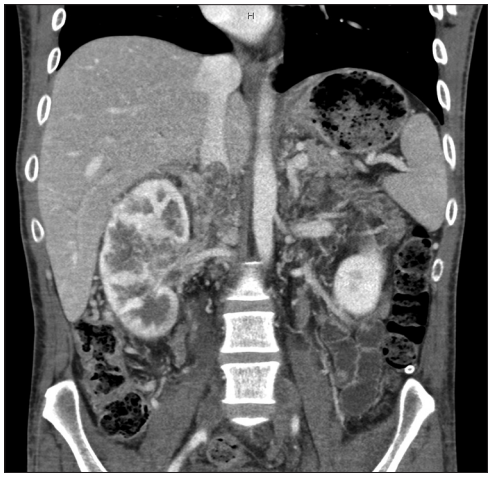

Figure 2: Obtained from the same patient in Figure 1, a coronal cut of computed tomography abdomen and pelvis with contrast in venous phase demonstrating inferior vena cava thrombus extending into retrohepatic inferior vena cava, Level IIIa

The Mayo group recently evaluated and internally validated the use of several radiologic features that correlate with the need for IVC reconstruction versus primary closure at the time of resection. These include the presence of a right-sided tumor, anteroposterior diameter of the IVC at the ostium of the renal vein (RVo) ≥24.0 mm, and radiologic identification of complete occlusion of the IVC at the RVo. For patients who have all three risk factors, the model predicts the need for IVC resection of 64%, however, if the patients had none of the specified features, there is a 98% chance of requiring cavorrhaphy alone.[12] Other variables include the level of the thrombus and specifically the presence of extension into the hepatic veins. In addition, we examined metastasis to the lungs or any other sites as well. IVC reconstruction therein refers to any repair requiring patch, grafting, or segmental excision with primary anastomosis. Cavotomy, with clot removal and cavorrhaphy, with or without bypass, was the default modality utilized when IVC reconstruction was not indicated.

Because urologists need to be critical of the imaging for surgical management, all CT or magnetic resonance imaging (MRI) data were reviewed by a single urologist (SO) and scored. As radiologic literature[13,14] consistently shows contrasted CT imaging to be equivalent to MRI in IVC thrombus characterization and measurement, no distinction or exclusion was made so long as at least one was available.

Statistical analysis

First, we investigated the Mayo Clinic risk factors for vascular reconstruction using the Chi-squared statistic. We then investigated the collected demographic data for associations with renal cancer mortality. We used univariate analysis to examine demographic factors for the final logistic regression mode and then employed a backward stepwise logistic regression for selection of the final model. The most significant factors were investigated using a time-to-event analysis (log-rank) and displayed in a Kaplan-Meier graph. Statistical analysis was performed using SPSS version 21 (IBM, Chicago, IL, USA).

RESULTS

Thirty-seven patients underwent nephrectomy and IVC tumor thrombectomy at two institutions from April 2007 to February 2015. Demographics are listed in Table 1. We noted a slightly male predominance and the relatively high number of Level II thrombus diagnoses (56.8, 21 of 37).

Factors predicting vascular reconstruction

In order to externally investigate the recent findings from the Mayo group, we labeled all men with the number of risk factors form their recent publication.[12] We found that risk factors of 0, 1, 2, and 3 and proportions of vascular reconstruction of 0%, 0%, 12.5%, and 13.6%, respectively (Chi-squared test $P = 0.788$, Figure 3).

Table 1: Demographics (*n*=37)

Demographic	Median (IQR) or *n* (%)
Age (years)	61.8 (50.5-72.6)
Gender	
Male	21 (56.8)
Female	16 (43.2)
AP diameter of IVC at the hepatic vein (mm)	40 (32.8-45.1)
AP diameter of IV at the renal vein (mm)	33.5 (27.3-40.0)
Mayo risk factors for vascular reconstruction	
0	3 (8.1)
1	4 (10.8)
2	8 (21.6)
3	22 (59.5)
Vascular reconstruction of the IVC	4 (10.8)
Lymph node dissection performed	30 (81.1)
Thrombus Level	
2	29 (78.4)
3	6 (16.2)
4	2 (5.4)
Invading the renal vein wall	16 (43.2)
Hepatic vein involvement	5 (13.5)
Pulmonary metastasis	5 (13.5)
Any metastasis	7 (18.9)
Clear cell histology	37 (100)
Furman grade	
1	0 (0)
2	8 (21.6)
3	19 (51.4)
4	10 (27)
Neoadjuvant chemotherapy	1 (2.7)
Overall mortality	8 (21.6)
Follow-up (months)	33.5 (9.4-128.6)

IQR: Interquartile range, IVC: Inferior vena cava

Factors predicting mortality

Our univariate and multivariate analysis of factors associated with mortality are demonstrated in Table 2. Note the predictable, and previously known mortality risk factors such as pulmonary metastases or any metastases correlated strongly in both univariate and multivariate analysis, whereas the Mayo risk factors did not. Any hepatic vein involvement (HVI) was the most significant determinate of death in multivariable analysis, controlling for the size of IVC at hepatics, pulmonary metastasis, and Fuhrman grade (logistic regression, $P = 0.02$). Due to HVI being the most significant factor, we investigated it in a time to event analysis and noted a significantly faster mortality rate (Log-rank $P = 0.002$, Figure 4).

DISCUSSION

Our results do not externally validate the Mayo risk factor system in predicting the need for IVC reconstruction in our limited sample, multi-institutional cohort… We interpret these findings to indicate the Mayo risk factor system may be institution dependent because the principles of assessment and repair of the IVC are not specifically standardized. While there are no explicitly agreed upon central tenets for

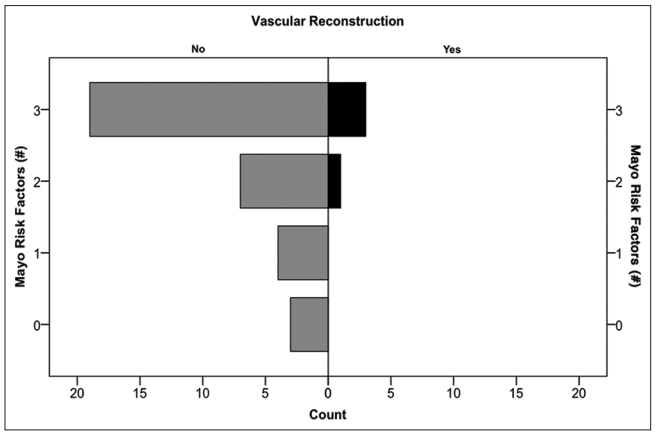

Figure 3: Pyramid graph displaying relationship the Mayo Clinic risk factors for vascular reconstruction (Chi-squared $P = 0.788$)

Table 2: Univariate and multivariate analysis describing factors associated with renal cancer mortality

Univariate		*P*
Age		0.36
AP diameter of the IVC at the hepatic vein (mm)		0.54
AP diameter of the IVC at the renal vein (mm)		0.93
Thrombus level		0.03
Mayo risks factors for reconstruction		0.87
Hepatic vein involvement		0.001
Pulmonary metastasis		0.001
Any metastasis		>0.001
Fuhrman grade <3		0.25
Invading the renal vein		0.66
Multivariate - logistic regression	**OR (95% CI)**	***P***
AP Diameter of the IVC at the hepatic vein (mm)	0.8 (0.7-1.0)	0.1
Hepatic vein involvement	138.6 (2.0-9429.7)	0.02
Pulmonary metastasis	40.7 (0.7-2369.8)	0.07
Fuhrman grade <3	0.4 (0.002-0.879)	0.04

OR: Odds ratio, CI: Confidence interval, AP: Anterior posterior, IVC: Inferior vena cava

IVC repair, general principles include: (1) Remove all tumor thrombus, (2) resect IVC wall as needed, and (3) ensure repair/reconstruction is tension free, watertight, and produces no appreciable decrease in diameter. Similarly, there is no consensus on what requires reconstruction and what does not. Therefore, it is possible the Mayo Clinic groups internally validated factors for reconstruction would not be universally predictive. In addition, our sample size may not be large enough to fully evaluate their predictive value. In attempts to ameliorate this, we combined retrospective cohorts from two institutions. This increased sample size as well as exposure to multiple institutional environments to mitigate single-center bias. In addition, each investigated each individual risk factor compared to RCC-specific survival and found no association in the Mayo risk factors, however, noted a significant association with HVI.

HVI identified on preoperative imaging did have a significant impact regarding cancer-specific mortality, and this to date has been unreported. Ciancio *et al*. alluded to this association and its moribund implications with their small retrospective

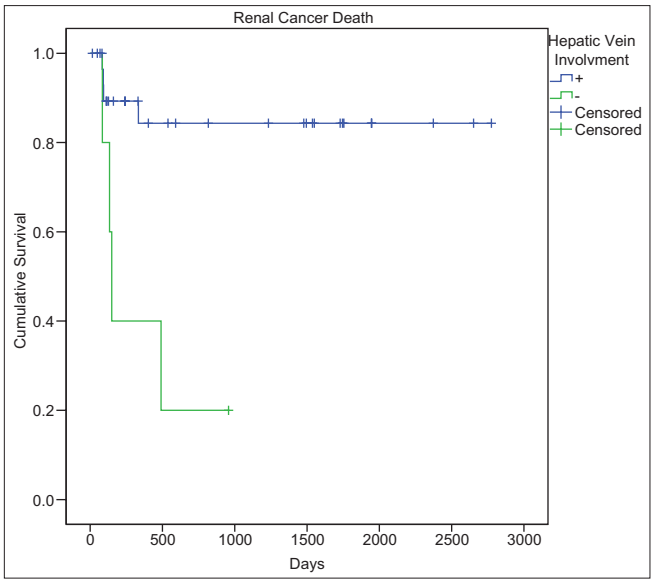

Figure 4: Kaplan–Meier curve displaying time to death from T3b-c renal cell carcinoma in the presence of hepatic vein involvement (log-rank $P = 0.002$)

cohort in 2001.[15] Interestingly, of their four patients, three of them were diagnosed with Budd–Chiari syndrome, a pathophysiologic state that none of our patients with HVI demonstrated. Only two of their patients were alive at 16 and 30 months follow-up, respectively. Their 50% overall survival at relatively short follow-up appears congruent with our data, both of which suggest that HVI is an indicator of aggressive and advanced disease. It is not apparent to the authors what, if any, known vascular mechanics or tumor biology that would differentiate less aggressive tumors to remain in the IVC, oftentimes en route to the right atrium, while more aggressive tumors would progress into the hepatic vein. We also assume that the tumors within the hepatic veins are more difficult to a removed within the liver vasculature and more likely lead to residual disease. Moreover, the secondary effects of hepatic vein congestion are likely to complicate an already morbid surgery by causing hepatic failure/inflammation, liver enlargement, ascites, lactic acidosis, and coagulation disorders.

The conventional wisdom from previous studies has suggested similar survival if tumor thrombus was successfully removed no matter the level.[3,6,16-21] A recent paper by Haddad *et al*. noted that contemporary surgical management in patients without metastasis who have RCC thrombus above the hepatic veins achieves a 50% 5-year survival.[1] Again, they noted no difference in Level III versus Level IV thrombus and survival. Unfortunately, invasion of tumor thrombus into the lumen of the hepatic vein was not assessed. If tumor thrombus into the hepatic veins is confirmed a significant indicator of death from renal cell cancer, this would indicate a significant deviation from the current paradigm. Future studies should include HVI as it may represent a risk factor that could influence future RCC

cancer staging and prompt neoadjuvant chemotherapy or the avoidance of surgery.

Study limitations include the retrospective nature of data collection. The radiologic findings identified in the Mayo risk factors were calculated retrospectively following surgical intervention. Whether or not the application of these factors in a prospective fashion would alter their predictive value is subject to debate. Our sample size is small and we combined retrospective cohorts from two academic institutions in an attempt to mitigate this effect. Given the relative rarity of the Level II–Level IV IVC thrombectomy, these cohorts would not be expected to be robust, though larger cohorts do exist in the literature. It should be reiterated that differences in surgical technique and institutional teaching could at least partially explain why the Mayo risk factors performed so poorly at predicting IVC reconstruction. Indeed, only four of the 37 patients received IVC reconstruction, as per our definition of it, which is approximately 10% or less than half as often as patients in the aforementioned Mayo study.

CONCLUSION

We were unable to validate the Mayo risk factors to predict vascular reconstruction in RCC patients with Level II–Level IV IVC thrombus undergoing IVC thrombectomy using radiologic endpoints. However, tumor thrombus traveling into the lumen of the hepatic veins was a significant risk for accelerated mortality.

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Conflicts of interest
There are no conflicts of interest.

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