Oncologic Outcomes Following Surgical Resection of Renal Cell Carcinoma with Inferior Vena Caval Thrombus Extending Above the Hepatic Veins: A Contemporary Multicenter Cohort

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Abbreviations and Acronyms

ALP = alkaline phosphatase
CSS = cancer specific survival
GFR = glomerular filtration rate
IVC = inferior vena cava
OS = overall survival
RCC = renal cell carcinoma
RFS = recurrence free survival

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Purpose: Suprahepatic inferior vena caval tumor thrombus in renal cell carcinoma cases has historically portended a poor prognosis. With advances in perioperative treatment of patients with high level thrombus contemporary outcomes are hypothesized to be improved. We evaluated long-term oncologic outcomes of contemporary surgical treatment of patients with renal cell carcinoma in whom level III-IV inferior vena caval thrombus was managed at high volume centers.

Materials and Methods: We examined clinical and pathological data on patients with renal cell carcinoma and level III-IV thrombus treated with surgery from January 2000 to June 2013 at 4 tertiary referral centers. Survival outcomes and associated prognostic variables were assessed by Kaplan-Meier and multivariate Cox regression analyses.

Results: We identified 166 patients, including 69 with level III and 97 with level IV thrombus. Median postoperative followup was 27.8 months. Patients with no evidence of nodal or distant metastasis (pN0/X, M0) had 5-year 49.0% cancer specific survival and 42.2% overall survival. There was no difference in survival based on tumor thrombus level or pathological tumor stage. Variables associated with an increased risk of death from kidney cancer on multivariate analysis were regional nodal metastases (HR 3.94, $p < 0.0001$), systemic metastases (HR 2.39, $p = 0.01$), tumor grade 4 (HR 2.25, $p = 0.02$), histological tissue necrosis (HR 3.11, $p = 0.004$) and increased preoperative serum alkaline phosphatase (HR 2.30, $p = 0.006$).

Conclusions: Contemporary surgical management achieves almost 50% 5-year survival in patients without metastasis who have renal cell carcinoma thrombus above the hepatic veins. Factors associated with increased mortality included nodal/distant metastases, advanced grade, histological necrosis and increased preoperative serum alkaline phosphatase. These findings support an aggressive surgical approach to the treatment of patients with renal cell carcinoma who have advanced tumor thrombus.

Key Words: kidney; carcinoma, renal cell; thrombosis; vena cava, inferior; mortality

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Renal cell carcinoma is the sixth most common malignancy in men and the eighth most common malignancy in women in the United States.[1] The proportion of patients with RCC who present with tumor extension into the renal vein and IVC is estimated to be as high as 10%, which has remained consistent despite the overall earlier diagnosis of RCC associated with increased use of cross-sectional imaging in recent years.[2,3] IVC involvement in RCC is associated with worse long-term survival compared to invasion of the renal vein only and if left untreated, most patients with RCC who have vena caval tumor thrombus die within 1 year.[4–7]

Tumor thrombus extending above the level of the hepatic veins (levels III and IV) develops infrequently and is noted in fewer than 1% of all RCC cases.[8] Patients who present with suprahepatic caval thrombus are at increased risk for perioperative morbidity and mortality.[9,10] Although some clinicians question the usefulness of surgery in patients with RCC who have advanced tumor thrombus, surgical excision remains the standard of care.

Due to its rarity outcomes in patients with high level thrombus (levels III and IV) have not been rigorously studied with only few patients with high level thrombus described in case series.[5,11,12] Further, many studies included patients treated several decades ago before the improvements and advances in perioperative and surgical technique in recent times. To address this shortcoming we evaluated survival outcomes and prognostic predictors in what is to our knowledge the largest reported contemporary series of patients with RCC and suprahepatic tumor thrombus treated at high surgical volume centers.

MATERIALS AND METHODS

Patients

Following institutional review board approval we reviewed the medical records to identify all patients with RCC who had level III or IV IVC tumor thrombus and underwent nephrectomy and vena caval thrombectomy between January 1, 2000 and June 30, 2013 at Mayo Clinic Rochester (62 patients), University of Texas M.D. Anderson Cancer Center (58), University of Texas Southwestern Medical Center at Dallas (25) and University of Wisconsin Hospital (21). Thrombus level was determined by transesophageal echocardiography or preoperative magnetic resonance imaging. Tumor thrombus level was classified according to the Novick classification, in which thrombus above the hepatic veins but below the diaphragm is level III and IVC thrombus above the diaphragm is level IV.[13]

Management, including neoadjuvant targeted therapy, preoperative angioembolization and intraoperative cardiopulmonary bypass, was at the discretion of the surgical team. Lymphadenectomy was also performed according to surgeon preference and did not follow a predefined template. Followup included physical examination, a complete serum biochemical panel and computerized tomography or ultrasound every 3 months in year 1 and semiannually thereafter.

Study Parameters

Patient parameters evaluated on univariate and multivariate analysis included age, gender, body mass index, current smoking history and ECOG (Eastern Cooperative Oncology Group) performance status (1-2 vs 3-4). Pathological characteristics included 2009 TNM pathological stage, grade, margin status (venous and nonvenous margins), tumor size (less than 7 vs 7 cm or greater) based on the largest measured pathological dimension and sarcomatoid features or coagulative tissue necrosis on histological examination. Due to the low number of grades 1 and 2 tumors we analyzed tumor grade as 1-3 vs 4. Preoperative laboratory parameters included in analysis were GFR (90 or greater vs less than 90 ml per minute), hematocrit (40% or greater vs less than 40% in males and 36% or greater vs less than 36% in females), calcium (10.3 or less vs greater than 10.3 mg/dl), platelet count (100 or greater vs less than 100×10^9/L), lactate dehydrogenase (194 or less vs greater than 194 IU/L), ALP (131 or less vs greater than 131 IU/L), albumin (3.2 or greater vs less than 3.2 gm/dl), alanine aminotransferase (35 or less vs greater than 35 IU/L), aspartate aminotransferase (35 or less vs greater than 35 IU/L) and total bilirubin (1.2 or less vs 1.2 mg/dl). The upper and lower limits of normal were based on accepted normal ranges for each serum parameter. GFR was calculated by the Cockcroft-Gault equation.

Statistical Analysis

Median RFS, CSS and OS were determined by Kaplan-Meier analysis. Cancer specific mortality was defined as death from RCC recurrence or metastasis and included all patients who died within 90 days perioperatively. Patients with evidence of clinical metastasis (M1) at presentation were excluded from RFS analysis. Multivariate Cox proportional hazard modeling was used to determine clinicopathological factors independently associated with recurrence and mortality. For multivariate analysis variables were selected if they were significant on univariate analysis. Two-sided $p < 0.05$ was considered significant. All statistical analysis was done with SPSS®, version 19.

RESULTS

Recurrence and Survival Outcomes

A total of 166 patients were identified who underwent surgery for RCC with IVC tumor thrombus extending above the hepatic veins. Supplementary table 1 (http://jurology.com/) and table 1 list clinical and pathological characteristics. Median age of the cohort was 62 years (range 24 to 84) and median followup was 27.8 months (range 1 to 148) in