

Original article

Prognosticators and outcomes of patients with renal cell carcinoma and adjacent organ invasion treated with radical nephrectomy

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Abstract

Objective: To study the natural history, prognosticators, and outcomes in patients with renal cell carcinoma (RCC) with extension of tumor beyond Gerota's fascia or invading contiguously into the adrenal gland (pT4) or both.

Patients and methods: From 1992 to 2012, we identified 61 patients who underwent radical nephrectomy and were found to have pT4 disease. Clinicopathologic variables were queried using univariate analysis to identify relevant prognostic variables. Cox proportional hazards model was used for multivariate analysis of predictors of cancer-specific survival. Survival plots were estimated using Kaplan-Meier method and survival analysis using log-rank test.

Results: Median age was 56 years (interquartile range: 49–64) and 49 (81.7%) patients had Eastern Cooperative Oncology Group Performance Status 0 or 1. At diagnosis, 22 (36.1%) patients showed nonmetastatic and 39 (63.9%) patients showed metastatic RCC. Overall, 49 (80.3%) patients had clear cell RCC, 24 (39.3%) patients had sarcomatoid features, and 39 (69.6%) patients had Fuhrman grade 3 to 4. There were 26 (42.6%) patients with pN0, 16 (26.2%) patients with pN1, and 19 (31.1%) patients with pNx. Median cancer-specific survival was 37 months for patients with nonmetastatic and 8 months for patients with metastatic RCC. On multivariate analysis, preoperative lactate dehydrogenase and alkaline phosphatase, M stage, pN stage, and sarcomatoid dedifferentiation were significantly associated with survival.

Conclusions: Survival in patients with pT4 remains poor. The pT4 disease is associated with a locally and regionally invasive biology that requires specific attention and warrants careful study. Understanding the drivers of this unique phenotype would generate therapeutic interventions that can change the behavior of these uniquely aggressive tumors. © 2016 Elsevier Inc. All rights reserved.

Keywords: T4; Renal cell carcinoma; Predictors; Nephrectomy; Surgery

1. Introduction

In 2015, 61,560 patients are estimated to be diagnosed with tumors of the kidney and renal pelvis in the United States, with 14,080 expected deaths [1], with renal cell carcinoma (RCC) being the most common tumor. The stage distribution of RCC has migrated because of the widespread use of abdominal imaging and now more than half are

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diagnosed as stage I. However, approximately 20% of patients would be diagnosed with stage IV disease [2], and large retrospective studies estimate the incidence of pT4 disease between 5% and 15% [3,4]. This subset of patients demonstrate poor outcomes with a 5-year survival rate of 20% to 30% and an estimated 10-year cancer-specific survival (CSS) rate of 12% [5,6]. Upfront aggressive surgery remains the standard of care for localized and locally advanced RCC and a cornerstone for the multimodal treatment of metastatic RCC [7,8]. Nevertheless, tumors with adjacent organ involvement pose a challenging scenario even for experienced surgeons. These tumors are often associated with aggressive features such as Fuhrman grade 3 or 4, sarcomatoid dedifferentiation, and lymphovascular invasion. Although several studies have shown promising results with preoperative therapy in the setting of large surgical tumor burden [9–11], such pathologic features ultimately result in an intrinsically aggressive behavior with adjacent organ invasion, potentially leading to “unresectable” disease in spite of the best targeted therapies available.

To our knowledge, there are no studies specifically investigating patients with pT4 RCC regardless of M stage. Moreover, there is paucity of data on the natural history of this high-risk population and the prognostic factors for survival. Our objective was therefore to study outcomes and prognostic variables (using *preoperative* and *postoperative* models) associated with survival in patients with pT4N0-1M0-1 RCC treated with radical nephrectomy (RN).

2. Patients and methods

2.1. Study population

This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center. A retrospective chart review was performed from an institutional kidney cancer database of patients diagnosed with RCC, who underwent RN at our institution from July 1992 to January 2012. We included patients with pT4 disease as defined by the 2010 TNM staging system [12]. As such, direct adrenal invasion, formerly classified as pT3a, was reassigned to pT4. Patients were included in this retrospective study if they underwent RN and were found to have pT4 on final pathology.

Demographics including age, gender, body mass index (BMI), Eastern Cooperative Oncology Group Performance Status, smoking history, and relevant symptoms were collected. Local symptoms included flank pain or hematuria and systemic symptoms included fever, night sweats, weight loss > 10 lb, or malaise. Palpable abdominal mass identified during preoperative physical examination in the ipsilateral flank region consistent with a renal mass was recorded. All patients underwent a metastatic evaluation including a chest computed tomography scan or chest X ray, cross-sectional abdominal imaging, and if indicated

bone scan or brain imaging. Clinical staging was based on the 2010 American Joint Committee on Cancer (AJCC) TNM staging system [12]. A dedicated genitourinary pathologist reviewed all available pathology slides. Tumor grade was determined using the Fuhrman grading system and tumor histology was reported according to the 2004 World Health Organization criteria [13]. Preoperative laboratory values such as lactate dehydrogenase (LDH), alkaline phosphatase, hemoglobin, and estimated Glomerular Filtration Rate were registered and characterized either as normal or abnormal based on standard institutional laboratory values. Surgical characteristics such as estimated blood loss and surgery duration for all patients were recorded. Systemic therapy administration and timing were at the discretion of the treating physician and were not standardized.

2.2. Study design

The primary objective of the study was to assess the outcomes of patients with RCC and adjacent organ invasion treated with RN. Our secondary objective was to establish predictors of CSS in this cohort of patients.

2.3. Data analysis

CSS was measured in months and defined as the time from date of nephrectomy to death of disease or last follow-up. The distribution of each categorical variable was summarized in terms of frequencies and percentages, and continuous nonparametric variables were summarized by median and interquartile range (IQR). Univariate (UVA) Cox proportional hazard regression model was performed to determine clinical and pathologic features associated with disease-specific death. From the existing covariates with statistical significance ($P < 0.05$) on UVA, we further developed 2 multivariate models to predict CSS after RN based on widely available preoperative and postoperative variables. Using the stepwise model selection, which requires 2 significant levels—one for adding variables and one for removing variables, we systematically examined all significant UVA variables and identified based on multivariate analysis (MVA) 2 separate models of preoperative and postoperative predictors of survival in patients with pT4 RCC. Survival curves were estimated according to Kaplan-Meier methods and were compared using the log-rank test. All analyses were carried out in SAS 9.3 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Clinical and pathologic characteristics

This study included 61 patients diagnosed with pT4 RCC treated with RN at our institution. Out of the 61 patients, 51 presented with single-organ invasion and 10

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