Comprehensive Assessment of the Impact of Cigarette Smoking on Survival of Clear Cell Kidney Cancer

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Purpose: The impact of modifiable environmental factors on kidney cancer specific outcomes is under studied. We evaluated the impact of smoking exposure on cancer specific survival in patients with clear cell renal cell carcinoma treated with surgery.

Materials and Methods: From a prospectively maintained database at a single center we collected the characteristics of 1,625 patients with clear cell renal cell carcinoma treated with surgery between 1995 through 2012. We determined the associations of smoking status with advanced disease, defined as AJCC (American Joint Committee on Cancer) stage greater than 2, and with cancer specific survival.

Results: The prevalence rate of current, former and never smoking at diagnosis was 16%, 30% and 54%, respectively. Of the patients 62% reported a smoking history of 20 pack-years or greater. Median followup in survivors was 4.5 years (IQR 2.2–7.9). On univariable analysis a smoking history of 20 pack-years or greater was associated with a significantly increased risk of advanced disease (OR 1.43, 95% CI 1.02–2.00). However, it did not achieve an independent association after adjusting for age and gender. Pathological stage and Fuhrman grade adversely affected cancer specific survival on multivariable competing risks analysis. Although the association between smoking and cancer specific survival did not achieve statistical significance on multivariable analysis, the direction of the central estimate (HR 1.5, 95% CI 0.89–2.52) suggested that smoking adversely impacts cancer specific survival. Current smokers faced a higher risk of death from another cause than never smokers (HR 1.93, 95% CI 1.29–2.88).

Conclusions: Smoking exposure substantially increases the risk of death from another cause and adversely impacts cancer specific survival in patients with clear cell renal cell carcinoma. Treatment plans to promote smoking cessation are recommended for these patients.

Key Words: kidney; carcinoma, renal cell; smoking; smoking cessation; nephrectomy

Abbreviations and Acronyms

ccRCC = clear cell RCC

RCC = renal cell carcinoma

VHL = von Hippel-Lindau

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Kidney cancer accounts for 2% of all incident malignancies worldwide with 64,770 cases and 13,570 deaths in the United States in 2012.[1] Increased cross-sectional imaging has contributed to the detection of incidental renal masses and the increase in favorable risk factors has resulted in

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a temporal trend suggesting improved survival.[2] Most strategies to improve kidney cancer survival have focused on optimizing the surgical technique and incorporating targeted therapy for metastatic disease with less attention to addressing modifiable risk factors such as cigarette smoking.[3] Therefore, if patients with RCC are experiencing improved cancer specific survival, more attention is needed for lifestyle strategies that impact overall mortality while smoking cessation requires more attention in survivorship programs.

Despite numerous epidemiological studies of RCC etiology risk factors for disease progression are still poorly understood. Cigarette smoking has been consistently associated with incidental ccRCC. Studies supporting a causal relationship have revealed a clear dose-response correlation and an observed benefit of smoking cessation on risk.[4,5]

A study of men with kidney cancer treated with nephrectomy recently suggested that smoking may be associated with an increased risk of cancer specific mortality.[6] Heavy smoking was independently associated with advanced pathological disease, indicating that cigarette smoking affects renal cell carcinogenesis and promotes disease progression.[6] Similarly, further investigation of molecular data in another retrospective study demonstrated that a history of smoking was associated with an increased risk of mutated *p53* and worse cancer specific survival after surgery.[7] These studies were limited by insufficient sample size to evaluate the impact of smoking on survival outcome or failure to quantify the intensity of smoking, including the number of cigarettes per day and smoking years. Furthermore, kidney cancer represents a heterogeneous class of tumors that arise from several cell types in the nephron and have distinctive natural histories. Previous studies combined all histological subtypes together, which may have obscured the risk of cigarette smoking, especially since the association between smoking and kidney cancer is primarily established for ccRCC.

We examined the impact of smoking status and cumulative smoking exposure on the risk of cancer specific death in 1,625 patients with ccRCC treated with partial or radical nephrectomy at a single high volume cancer center.

MATERIALS AND METHODS

Patient Selection

Data on 3,155 consecutive patients with RCC who underwent partial or radical nephrectomy between 1995 and 2012 were obtained from a prospectively maintained clinical database. Genitourinary surgeons performed radical nephrectomy according to standard protocol, which involves excision of the kidney along with the Gerota fascia. Partial nephrectomy was similarly performed by excising the tumor and adjacent normal parenchyma. The hilar and regional lymph nodes adjacent to the ipsilateral great vessels were resected as needed, along with enlarged lymph nodes that were identified on preoperative computerized tomography or were palpable intraoperatively.

The institutional review board approved the request to exempt this retrospective study and approved waivers for Health Insurance Portability and Accountability Act authorization and informed consent. Patients were excluded from analysis if they died at operation (4), had a nonccRCC histology (1,004) or incomplete data on smoking history (512), or presented with metastatic disease (10), resulting in a total sample size of 1,625.

Pathological Evaluation

Surgical specimens were processed using standard pathological techniques and reviewed by experienced genitourinary pathologists. All specimens were histologically confirmed to be ccRCC. Tumors were staged according to the 2007 AJCC TNM classification.[8] Tumor grading was done using the Fuhrman system.[9]

Followup Regimen

Patients were seen 1 month after surgery, every 6 months for the first 2 years and annually thereafter. Followup consisted of history, physical examination, serum chemistry studies, chest radiography and renal ultrasound. The followup regimen was personalized based on pathological characteristics and surgical technique. Cause of death was determined by chart review, corroborated by death certificates and agreed on by an interdisciplinary conference.

Smoking Exposure

Self-reported smoking data were routinely collected on all patients at diagnosis using a smoking specific questionnaire. Variables available for analysis included smoking status (current, former or never smoker), smoking duration (fewer than 20, 20 to 39 and 40 years or greater) and quantity of cigarettes smoked (1 to 10, 11 to 20, 21 to 30 and greater than 30 per day). Smoking status was determined at diagnosis. Current smokers were defined as active smokers or those who had stopped smoking within 1 year of diagnosis. Patients were identified as former smokers if they had stopped smoking at least 1 year before diagnosis based on previously published definitions.[10] Smoking duration and number of cigarettes per day were used to derive the pack-years smoked (fewer than 20 vs 20 or greater) as a measure of cumulative smoking exposure for all former and current smokers.

Statistical Analysis

Descriptive statistics were calculated for demographic, disease and smoking characteristics. Associations between categorical variables were assessed using the chi-square test and the Kruskal-Wallis test was used for continuous variables. Followup was calculated from the date of diagnosis. Because smoking is an established risk factor for common health problems that increase the risk of death, we performed competing risks analysis. The cumulative incidence was estimated with cancer specific