Diabetes Mellitus is Independently Associated with an Increased Risk of Mortality in Patients with Clear Cell Renal Cell Carcinoma

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Abbreviations and Acronyms

BMI = body mass index
CCI = Charlson comorbidity index
ccRCC = clear cell RCC
CKD = chronic kidney disease
CSS = cancer specific survival
DM = diabetes mellitus
ECOG = Eastern Cooperative Oncology Group
eGFR = estimated glomerular filtration rate
IGF-1 = insulin-like growth factor-1
OS = overall survival
PFS = progression-free survival
RCC = renal cell carcinoma

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For other articles on related topics see pages 1822, 1831 and 1842.

Purpose: Conflicting data exist on the interaction of diabetes mellitus with outcomes in patients with renal cell carcinoma. We evaluated the association of diabetes mellitus with survival in patients with clear cell renal cell carcinoma treated with nephrectomy.

Materials and Methods: We reviewed the records of 1,964 patients treated surgically for sporadic, unilateral, M0 clear cell renal cell carcinoma between 1990 and 2008. One pathologist re-reviewed all specimens to confirm clear cell renal cell carcinoma. We matched 257 patients with diabetes 1:2 to referent patients without diabetes according to clinicopathological and surgical features. Cancer specific and overall survival was estimated using the Kaplan-Meier method. Cox models were used to evaluate associations with outcomes.

Results: A total of 257 patients (13%) had diabetes mellitus. They were significantly older and more likely to be obese, and had higher Charlson scores, renal impairment and smoking rates, and worse performance status at surgery ($p < 0.001$). Pathological features were similar between the groups. Median postoperative followup was 8.7 years. Five-year cancer specific survival was similar in patients with and without diabetes (82% vs 86%, $p = 0.1$) while 5-year overall survival was significantly worse in those with diabetes (65% vs 74%, $p < 0.001$). On multivariable analysis diabetes mellitus independently predicted cancer specific mortality (HR 1.55, 95% CI 1.08–2.21, $p = 0.02$) and all-cause mortality (HR 1.32, 95% CI 1.06–1.64, $p = 0.01$).

Conclusions: Our results suggest that diabetes mellitus is independently associated with decreased cancer specific and overall survival in patients with surgically treated clear cell renal cell carcinoma.

Key Words: kidney; carcinoma, renal cell; diabetes mellitus; nephrectomy; mortality

The incidence of RCC has steadily increased in the last 4 decades, accounting for 65,150 new cases and 13,680 deaths in 2013.[1] Obesity, smoking and hypertension are well described risk factors for RCC.[2,3] The increasing prevalence of obesity and hypertension in the United States may help explain the increasing incidence of RCC. Because DM is frequently linked to obesity and hypertension as part of the metabolic syndrome, investigators have queried the potential prognostic role of DM in patients with RCC.

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Coincident with the increasing incidence of RCC the incidence of DM has been increasing worldwide.[4] The hallmark of DM is hyperinsulinemia with concurrent over expression of IGF-1, inflammatory cytokines and reactive oxygen species, which results in dysregulation of cell proliferation and tumorigenesis.[5] Numerous meta-analyses have identified an increased incidence of solid tumors in patients with DM.[6–8] However, the prognostic impact of DM in RCC remains unclear with published reports supporting the increased risk of recurrence and disease specific death in those with DM who have RCC.[9,10] This is counterbalanced by others who dispute any independent association between DM and RCC specific outcomes.[11–14]

However, prior studies were limited by smaller sample sizes and insufficient power to account for important confounders such as coexisting comorbidity, obesity and pathological characteristics. Thus, we evaluated the association of DM with outcomes in a large cohort of patients with ccRCC treated surgically who had long-term postoperative followup.

METHODS

Patient Selection

After receiving institutional review board approval we queried the renal tumor registry at our institution and identified 1,964 consecutive patients treated surgically for sporadic, unilateral, nonmetastatic ccRCC between 1990 and 2008 (fig. 1). Patients were classified with DM according to preoperative medical records.

Clinical and Pathological Features

The clinical features studied included patient age, gender, surgery year and type, preoperative symptoms, smoking status, serum creatinine, eGFR calculated using the MDRD (Modification of Diet in Renal Disease) formula, CKD stage (defined as glomerular filtration rate 60 or greater, 45 or greater to less than 60, 30 or greater to less than 45, 15 or greater to less than 30 and less than 15 ml/minute/1.73 m^2), ECOG performance status, CCI including and excluding the diabetic component, BMI and obesity (defined as BMI 30 kg/m^2 or greater). The cohort was restricted to ccRCC due to the preponderance of ccRCC and the inability to adequately balance other histological subtypes between patients with and without DM. Pathological features, including tumor size, 2009 AJCC (American Joint Committee on Cancer) TNM classification, nuclear grade, coagulative tumor necrosis and sarcomatoid differentiation, were assigned after blinded rereview of all surgical specimens by 1 urological pathologist (JCC). In each patient we calculated the Mayo Clinic PROG (prognosis) score,[15] which indicates the risk of progression to metastatic disease in patients with ccRCC, and the Mayo Clinic SSIGN (stage, size, grade and necrosis) score,[16] which is prognostic of the risk of death from ccRCC.

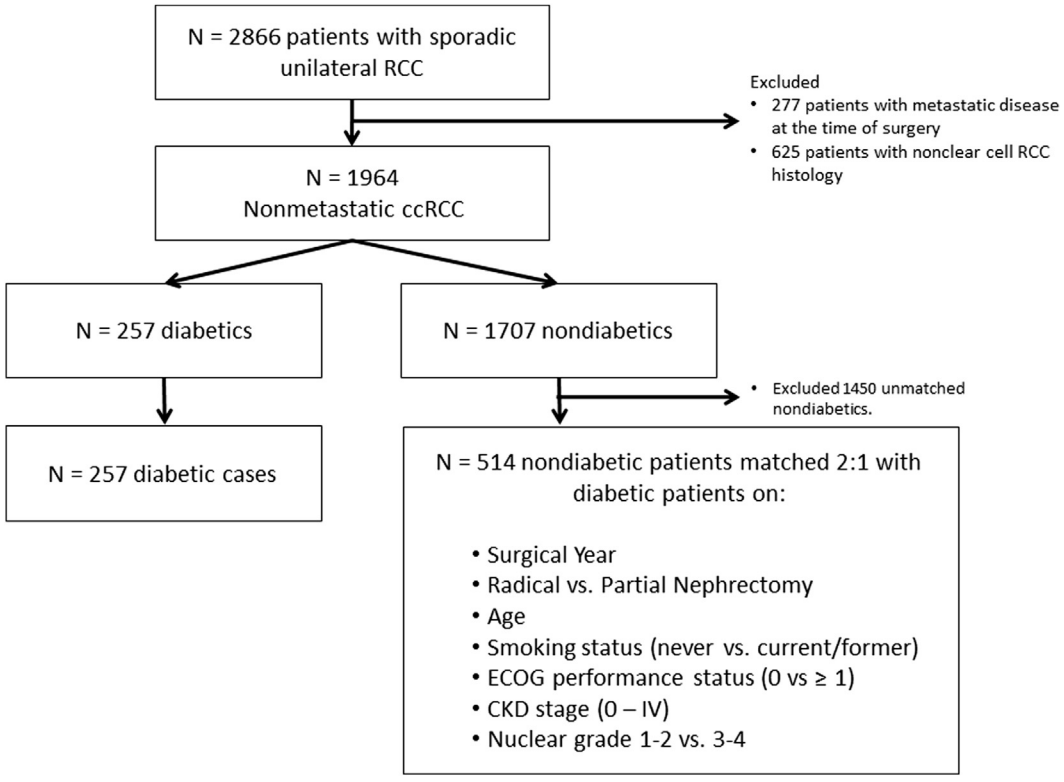

Figure 1. Selection of diabetic and matched nondiabetic cohorts from all patients with ccRCC treated between 1990 and 2008.