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Survival and Functional Stability in Chronic Kidney Disease Due to Surgical Removal of Nephrons: Importance of the New Baseline Glomerular Filtration Rate

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Abstract

Background: Chronic kidney disease (CKD) can be associated with a higher risk of progression to end-stage renal disease and mortality, but the etiology of nephron loss may modify this. Previous studies suggested that CKD primarily due to surgical removal of nephrons (CKD-S) may be more stable and associated with better survival than CKD due to medical causes (CKD-M).
Objective: We addressed limitations of our previous work with comprehensive control for confounding factors, differentiation of non–renal cancer-related mortality, and longer follow-up for more discriminatory assessment of the impact of CKD-S.
Design, setting, and participants: From 1999 to 2008, 4299 patients underwent surgery for renal cancer at a single institution. The median follow-up was 9.4 yr (7.3–11.0). The new baseline glomerular filtration rate (GFR) was defined as the highest GFR between the nadir and 42 d after surgery. Three cohorts were retrospectively evaluated: no CKD (new baseline GFR >60 ml/min/1.73 m^2); CKD-S (new baseline GFR<60 but preoperative >60 ml/min/1.73 m^2); and CKD-M/S (new baseline and preoperative GFR both <60 ml/min/1.73 m^2). Cohort status was permanently set at 42 d after surgery.
Intervention: Renal surgery.
Outcome measurements and statistical analysis: Decline in renal function (50% reduction in GFR or dialysis), all-cause mortality, and non–renal cancer mortality were examined using a multivariable Cox proportional hazards model.
Results and limitations: CKD-M/S had a higher incidence of relevant comorbidities and the new baseline GFR was lower. On multivariable analysis (controlling for age, gender, race, diabetes, hypertension, and cardiac disease), CKD-M/S had higher rates of progressive decline in renal function, all-cause mortality, and non–renal cancer mortality when compared to CKD-S and no CKD (hazard ratio [HR] 1.69–2.33, all $p < 0.05$). All-cause mortality was modestly higher for CKD-S than for no CKD (HR 1.19, $p = 0.030$), but renal stability and non–renal cancer mortality were similar for these groups. New baseline GFR of <45 ml/min/1.73 m^2 significantly predicted adverse outcomes. The main limitation is the retrospective design.
Conclusions: CKD-S is more stable than CKD-M/S and has better survival, approximating that for no CKD. However, if the new baseline GFR is <45 ml/min/1.73 m^2, the risks of functional decline and mortality increase. These findings may influence counseling for

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patients with localized renal cell carcinoma and higher oncologic potential when a normal contralateral kidney is present.
Patient summary: Survival is better for surgically induced chronic kidney disease (CKD) than for medically induced CKD, particularly if the postoperative glomerular filtration rate is ≥45 ml/min/1.73 m^2. Patients with preexisting CKD are at risk of a significant decline in kidney function after surgery, and kidney-preserving treatment should be strongly considered in such cases.

1. Introduction

It is widely accepted that chronic kidney disease (CKD) includes all patients with a glomerular filtration rate (GFR) of <60 ml/min/1.73 m^2 or structural/functional abnormalities that persist for >90 d, irrespective of etiology [1]. This definition was first proposed in 2002 to address worldwide under-recognition of a disease associated with significant potential short- and long-term risks [1]. CKD has been linked to increased cardiovascular morbidity and all-cause mortality in large population-based studies, even when controlling for confounding factors [2–4]. Recent research suggests that certain CKD cohorts tend to retain stable function and have lower associated risks, which could have implications for the management of patients with renal cancer [5,6]. The Kidney Disease: Improving Global Outcomes (KDIGO) group released new clinical practice guidelines for the evaluation and management of CKD in 2013 [7,8], and a new schema for CKD classification has been proposed in which CKD is categorized according to cause, GFR, and the presence of albuminuria [7,8].

However, details regarding how CKD etiology affects evaluation, management, and prognosis are not well defined in the KDIGO guidelines. Our research in the area of CKD primarily due to surgical removal of nephrons (CKD-S) suggests that this disease entity may be associated with a lower risk of CKD progression and improved overall survival when compared to CKD with medical etiology (CKD-M) [6,9]. Limitations of our prior work included a lack of data regarding cause of death and only intermediate-term follow-up. In the present study, we provide extended follow-up regarding the impact of CKD-S on renal function, overall survival, and non–renal cancer survival relative to patients with CKD-M and those with no CKD, including a more comprehensive analysis of confounding factors.

2. Patients and methods

The Cleveland Clinic kidney surgery registry was used to identify all patients who underwent renal cancer surgery from 1999 to 2008. Patients younger than 18 yr and those who underwent nephrectomy for reasons other than suspected cancer were excluded. The treating surgeon determined the surgical approach according to individual characteristics, generally opting for nephron-sparing surgery (NSS) whenever feasible [10,11].

All serum creatinine (sCr) values were extracted from the electronic medical records and CKD-EPI equations were used to estimate GFR. CKD was staged according to National Kidney Foundation guidelines [12]. Baseline renal function was defined as the most recent GFR preceding surgery, nadir renal function as the lowest GFR after surgery, new baseline renal function as the highest GFR obtained between the nadir and 42 d after surgery, and latest renal function as the most recent follow-up GFR. The cohort status of no CKD (preoperative and new baseline GFR both >60 ml/min/1.73 m^2), CKD-S (new baseline GFR <60 but preoperative >60 ml/min/1.73 m^2), or CKD-M/S (new baseline and preoperative GFR both <60 ml/min/1.73 m^2) was permanently set at 42 d after surgery.

Renal function decline was defined as the percentage GFR loss after surgery ([new baseline GFR – latest GFR]/new baseline GFR × 100%). Cause of death was defined as progressive renal cancer or otherwise; differentiation of other causes, such as cardiac, could not be reliably determined. Patients experiencing any of these events before 42 d after surgery were excluded from the study.

Continuous variables are reported as median (interquartile range) and categorical variables as frequency (%). ANOVA was used to compare continuous and Chi-square test for categorical variables. When the normality assumption was violated, we used nonparametric tests as appropriate. Statistical significance was based on a two-sided significance level of 0.05. The main endpoints of the study were interval to a 50% decline in GFR or dialysis [13], non–renal cancer mortality, and all-cause mortality. We constructed cumulative incidence curves for each event stratified by CKD-M/S, CKD-S, and no CKD groups. We then fit multivariable Cox proportional hazards models adjusted for age, gender, race, and comorbidities. A priori interactions between renal function, hypertension, and diabetes mellitus were examined. Restricted cubic splines with five knot locations (5, 27.5, 50, 72.5, and 95 percentiles) were used to account for nonlinear associations between continuous variables and the outcome measured. We avoided stepwise variable selection, and our variable-to-event ratio was >14, accounting for degrees of freedom spent for cubic splines and interaction terms. For time to event analyses, we reported median follow-up for subjects without events. We used competing-risk cumulative incidence curves and regression analyses to examine the impact of etiology of CKD on (1) renal function decline, accounting for all-cause mortality as a competing risk; and (2) non–renal cancer mortality, accounting for renal cancer mortality as a competing risk. All statistical analyses were performed using SAS v.9.3 (SAS Institute, Cary, NC, USA) and R v.3.1.2 (www.R-project.org).

3. Results

Among 4299 patients who underwent surgery for suspected renal cancer, 55% had CKD after surgery, including 1113 with GFR <60 ml/min/1.73 m^2 only after surgery (CKD-S) and 1237 with GFR <60 ml/min/1.73 m^2 both before and after surgery (CKD-M/S). Significant differences in the baseline characteristics of the groups of patients with no CKD, CKD-S, and CKD-M/S are evident (Table 1). For example, patients with CKD-M/S were older and more likely to have relevant comorbidities. The median preoperative GFR was 91, 75, and 48 ml/min/1.73 m^2 in the no CKD, CKD-S, and CKD-M/S groups, respectively. The corresponding new baseline GFR after surgery was 79, 49, and 38 ml/min/1.73 m^2, representing a median GFR loss of 8, 29, and 6 units. Table 2 provides