

# Long-Term Renal Function Outcomes after Radical Cystectomy

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**Purpose:** We evaluated the long-term natural history of renal function after radical cystectomy with urinary diversion and determined factors associated with decreased renal function.

**Materials and Methods:** We reviewed the records of 1,631 patients who underwent radical cystectomy between 1980 and 2006. The estimated glomerular filtration rate was calculated preoperatively and at various intervals after surgery. A renal function decrease was defined as a greater than 10 ml per minute/1.73 m<sup>2</sup> reduction in the estimated glomerular filtration rate. Multivariate analysis was done to evaluate the association of clinicopathological features, incontinent vs continent diversion type and postoperative complications with decreased renal function.

**Results:** A total of 1,241 patients (76%) underwent incontinent diversion and 390 (24%) underwent continent diversion. Median followup after radical cystectomy in patients alive at last followup was 10.5 years (IQR 7.1, 15.3). The median preoperative estimated glomerular filtration rate was higher in the continent diversion cohort (67 vs 59 ml per minute/1.73 m<sup>2</sup>,  $p < 0.0001$ ). This difference was maintained until 7 years postoperatively, after which no difference was noted in renal function by diversion type. By 10 years after radical cystectomy the risk of a renal function decrease was similar for incontinent and continent diversion (71% and 74%, respectively,  $p = 0.13$ ). On multivariate analysis risk factors associated with decreased renal function included age (HR 1.03,  $p < 0.0001$ ), preoperative estimated glomerular filtration rate (HR 1.05,  $p < 0.0001$ ), chronic hypertension (HR 1.2,  $p = 0.01$ ), postoperative hydronephrosis (HR 1.2,  $p = 0.03$ ), pyelonephritis (HR 1.3,  $p = 0.01$ ) and ureteroenteric stricture (HR 1.6,  $p < 0.0001$ ).

**Conclusions:** Decreased renal function is noted in most patients during long-term followup after radical cystectomy. Postoperative hydronephrosis, pyelonephritis and ureteroenteric stricture represent potentially modifiable factors associated with a decrease. Choice of urinary diversion was not independently associated with decreased renal function.

**Key Words:** urinary bladder neoplasms; urinary diversion; renal insufficiency, chronic; cystectomy; postoperative complications

IN 2013 bladder cancer represented the fifth most commonly diagnosed malignancy in the United States.<sup>1</sup> RC

with UD remains the standard of care for muscle invasive bladder cancer and high risk nonmuscle invasive

## Abbreviations and Acronyms

CD = continent diversion  
CKD = chronic kidney disease  
eGFR = estimated GFR  
GFR = glomerular filtration rate  
ID = incontinent diversion  
RC = radical cystectomy  
RF = renal function  
UD = urinary diversion

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disease.<sup>2</sup> Nevertheless, RC is associated with significant risks of perioperative and long-term morbidity and mortality.<sup>3,4</sup> UD is particularly associated with subsequent deterioration in RF.<sup>3-6</sup>

RF deterioration is particularly concerning, given the noted association between severe CKD and all cause mortality.<sup>4,6-11</sup> The etiology of an RF decrease after RC is likely multifactorial, including age related changes, potential nephrotoxic chemotherapy, the impact of patient comorbidities, which are frequent in such a population, and postoperative urinary tract obstruction and infectious related complications.

However, in most studies of RF after UD to date serum creatinine was used as the measure of RF.<sup>4,8,10-13</sup> Serum creatinine is influenced by numerous factors, including age, gender, hydration level and muscle mass, and it often overestimates the GFR. Because most patients treated with RC and UD are elderly, in this population serum creatinine may be particularly inaccurate. Quantifying RF by eGFR is a more accurate measure of RF since it accounts for additional relevant variables such as age, race and gender.<sup>14</sup>

In this context we determined the long-term natural history of RF, as measured by eGFR in patients who underwent RC with UD. We also identified potentially modifiable factors associated with worsening RF in these patients.

## MATERIALS AND METHODS

After receiving institutional review board approval we identified 2,472 patients treated with RC and UD for pTanyNanyM0 bladder cancer at our institution between 1980 and 2006. Of these patients we excluded 236 without serum creatinine measurement within 90 days preoperatively, 589 without serum creatinine measurement 90 days or greater postoperatively and 16 without research authorization, leaving 1,631 available for analysis.

All patients underwent RC using standard techniques. The ID group consisted of those who received an ileal conduit while the CD group included 5 patients with cutaneous CD and 385 with orthotopic neobladder diversion. The ureteroenteric anastomosis was formed using a freely refluxing technique for ID and CD.

Evaluated clinical variables included age, race, gender, ECOG (Eastern Cooperative Oncology Group) performance status, preoperative chronic hypertension, type 2 diabetes, preoperative hydronephrosis, baseline and followup eGFR, receipt of perioperative systemic chemotherapy and UD type. When evaluating postoperative complications, we focused on those related to renal obstruction or infection, that is hydronephrosis, pyelonephritis, urolithiasis, recurrent urinary tract infection (4 or more per year), ureteroenteric stricture, stomal stenosis and renal unit loss. The designation of hydronephrosis was based on abnormal upper tract imaging in patients

with or without documentation of a ureteroenteric stricture. Pyelonephritis was defined as a febrile episode with a positive urine culture in the absence of another indication for fever. We previously reported our method of identifying long-term complications of UD.<sup>4</sup>

The retrospective nature of our study precluded standardized postoperative surveillance in all patients. However, followup after RC at our institution is recommended quarterly for the first 2 years after surgery, semiannually for the next 2 years and annually thereafter in patients without evidence of recurrence. For patients followed elsewhere the cystectomy registry at our institution monitors outcomes annually by correspondence with the patient and treating physician.

The primary outcome measure was eGFR. It was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equations because these equations provide the most accurate assessment of RF, with the best prediction of long-term patient outcome and the least bias over a large eGFR range.<sup>14-17</sup> To evaluate factors associated with a decrease in eGFR we compared preoperative eGFR to values obtained at subsequent postoperative visits. For the 6-month postoperative time point we used serum creatinine measurements made 3 to 9 months after surgery. For the 1-year time point we evaluated serum creatinine measured 9 to 18 months postoperatively. For all subsequent time points values obtained within 6 months of the given time point were considered. If multiple serum creatinine values were available for a given time point, we used the median for analysis. We assessed for a RF decrease, defined as a greater than 10 ml per minute/1.73 m<sup>2</sup> reduction in eGFR from baseline during followup to be consistent with a recent similar analysis.<sup>18</sup> On time dependent analysis we evaluated the time since surgery for the RF decrease.

Continuous variables are shown using summary statistics and categorical variables are shown as the frequency. Median eGFR values were compared using the Wilcoxon rank sum test. The rate of RF decrease-free survival was estimated using the Kaplan-Meier method and compared using the log rank test. Cox proportional hazards regression models were used to assess the association of clinicopathological variables with decreased RF.

Statistical analysis was done using SAS® and R (R Foundation for Statistical Computing, Vienna, Austria) with 2-sided  $p < 0.05$  considered statistically significant.

## RESULTS

Table 1 lists patient clinicopathological features. A total of 1,241 and 390 patients underwent ID and CD, respectively. Demographic differences between the ID and CD cohorts were noted for almost all evaluated variables, including age at surgery, preoperative eGFR, T and N stage, functional status and comorbidities. Of 1,631 patients 192 (12%) received chemotherapy perioperatively, including cisplatin based regimens in 146 (76%). Overall 888 patients (54%) experienced 1 or more

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