Long-term Renal Function following Radical Cystectomy for Bladder Cancer

Maja Vejlgaard, Sophia L. Maibom, Hein V. Stroomberg, Alicia M. Poulsen, Peter O. Thind, Martin A. Røder, Ulla N. Joensen

PII: S0090-4295(21)01083-9
DOI: https://doi.org/10.1016/j.urology.2021.11.015
Reference: URL 23241

To appear in: Urology

Received date: 27 August 2021
Revised date: 6 October 2021
Accepted date: 9 November 2021

Please cite this article as: Maja Vejlgaard, Sophia L. Maibom, Hein V. Stroomberg, Alicia M. Poulsen, Peter O. Thind, Martin A. Røder, Ulla N. Joensen, Long-term Renal Function following Radical Cystectomy for Bladder Cancer, Urology (2021), doi: https://doi.org/10.1016/j.urology.2021.11.015

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc.
Long-term Renal Function following Radical Cystectomy for Bladder Cancer

Maja Vejlgaard\textsuperscript{a}, Sophia L. Maibom\textsuperscript{a,b}, Hein V. Stroomberg\textsuperscript{a}, Alicia M. Poulsen\textsuperscript{a}, Peter O. Thind\textsuperscript{a}, Martin A. Røder\textsuperscript{a,b}, Ulla N. Joensen\textsuperscript{a,b}

\textsuperscript{a} Department of Urology, Centre for Cancer and Organ Diseases, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
\textsuperscript{b} Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Declarations of interest: none

Key words: bladder cancer, radical cystectomy, renal function, renal insufficiency, long-term complications

Word count:
Abstract: 249
Manuscript text: 2985

*Corresponding author:
Maja Vejlgaard
Copenhagen Prostate Cancer Centre
Ole Maaloes Vej 24, unit 7521
DK-2200 Copenhagen N
Telephone number: +45 20 11 56 14
maja.vejlgaard.02@regionh.dk
Abstract

Objectives: To evaluate long-term renal function following radical cystectomy (RC) for bladder cancer and identify risk factors associated with postoperative decline in renal function.

Methods: The study included patients who underwent RC at a single centre in Denmark between 2009 and 2019. Data was collected through national electronic medical records. Renal function was evaluated by estimated glomerular filtration rate (eGFR) using pre- and postoperative creatinine measurements. Cumulative incidence and Cox Proportional Hazards models were used to describe the loss of renal function and its association with clinicopathological variables, as well as its effect on mortality.

Results: After exclusions, 670 patients were eligible for analyses. Median follow-up time was 6.2 years (interquartile range 4.0-8.4). The proportion of patients with renal insufficiency (eGFR<45 mL/min) increased from 8.9% before RC to 19% five years after surgery. A total of 610 patients with preoperative eGFR≥45 were included in survival analyses. The absolute risk of renal function decline to CKD stage G3b or worse (eGFR<45 mL/min) was 17% (95% CI 14-20) at five years postoperatively. Loss of renal function was not significantly associated with higher all-cause mortality. In multivariate analysis lower preoperative eGFR, diabetes mellitus, prior pelvic radiation therapy, continent urinary diversion types, and postoperative ureteral stricture were all independently associated with renal function decline.

Conclusions: The long-term renal function decreases considerably for a large number of RC patients. Recognizing preoperative risk factors could identify patients who benefit from enhanced renal surveillance or early intervention for modifiable factors to minimize renal insufficiency following RC.

Keywords

Bladder cancer; radical cystectomy; renal function; Renal insufficiency; long-term complications
Introduction

Currently, radical cystectomy (RC) with urinary diversion represents the standard of care for muscle-invasive bladder cancer (BC) and selected high-risk non-muscle-invasive BC in patients who are fit for major surgery.\(^1\) It is a complex surgical procedure with a high risk of perioperative and long-term complications.\(^2\) We have recently reported short-term morbidity following RC at our institution.\(^3\) RC entails a risk of renal deterioration, which has important implications for the management of recurrent disease and quality of life. Loss of renal function can occur as a result of ureteral strictures or voiding problems in continent diversions, urinary tract infections, stone formation, and comorbidity.\(^4\) Furthermore, patients undergoing RC may be exposed to therapy that affects kidney function, such as nephrototoxic chemotherapy during induction or neoadjuvant therapy before RC. Chronic kidney disease is associated with frequent and prolonged hospitalizations, risk of cardiovascular diseases, increased drug dependency, and higher all-cause mortality.\(^5\)

Additionally, impaired renal function following RC may reduce the possibility of receiving life-prolonging secondary cancer therapy such as chemo- or immunotherapy. Monitoring of renal function after RC is paramount to detect any renal function decline and alleviate reversible causes or avoid further deterioration. Nevertheless, it remains controversial how renal function should be assessed during follow-up.

Several studies have investigated the decline in renal function after RC, but due to a heterogeneity of patient cohorts in terms of data collection methods, follow-up time, and definitions of renal insufficiency no large-scale analyses have been made.\(^6\)\(^-\)\(^12\) The aim of this study is to investigate the loss of renal function. We aim to describe postoperative renal function and identify patient
characteristics and postoperative factors associated with renal deterioration in BC patients who underwent RC over a decade at our institution with careful long-term follow-up.

Methods

All BC patients undergoing RC at the Department of Urology, Rigshospitalet, Denmark between December 2009 and June 2019 were identified. Exclusion criteria can be seen in Supplementary Figure 1. Follow-up was obtained on the March 26th, 2021.

Radical cystectomy included the removal of the bladder and internal genital organs, as well as an extended pelvic lymph node dissection. Patients who underwent surgery between 2009 and 2012 received an open procedure RC. After 2012, RC was performed either as an open or robot-assisted laparoscopic procedure. All patients residing in Denmark were followed according to national guidelines to detect recurrence of disease and were offered long-term follow-up at our institution with yearly evaluations of kidney function by radioisotope renography scan and/or creatinine measurements, as clinically indicated.

Clinicopathological variables, creatinine measurements, hospitalizations, and deaths were collected through a manual review of the Danish national Electronic Medical Record (EMR), which gathers data across all hospitals nationally. The Charlson Comorbidity Index (CCI) was calculated excluding the criteria “any malignancy without metastasis” and without age-adjustment. Patients
were defined as having preoperative chronic hypertension and diabetes mellitus if they received respectively antihypertensive or antidiabetic medication at the time of RC. Development of ureteral stricture was defined by the need for postoperative renal catheterization, including nephrostomy and ureteral stents, performed either as a temporary or permanent treatment.

Renal function was evaluated by the estimated Glomerular Filtration Rate (eGFR) and calculated using the Chronic Kidney Disease Epidemiology Collaboration Equation for eGFR. Chronic Kidney Disease (CKD) stage was defined according to K/DOQI guidelines by the calculated eGFR: CKD stage grade 1 (G1) ≥ 90 mL/min per 1.73m², grade 2 (G2) = 60-89 mL/min per 1.73m², grade 3a (G3a) = 45-59 mL/min per 1.73m², grade 3b (G3b) = 30-44 mL/min per 1.73m², grade 4 (G4) = 15-29 mL/min per 1.73m², and grade 5 (G5) < 15 mL/min per 1.73m² (Table 1). Preoperative CKD stage was determined based on the plasma creatinine (p-Creatinine) measured the day before surgery. Postoperatively, we registered the most recent p-Creatinine measurement before end of follow-up, as well as measurements at all times where alterations in eGFR caused a change in CKD stage, without a subsequent change back to the prior stage, thereby excluding admissions where a temporary drop in eGFR occurred due to acute illness. We defined the date of change in CKD stage as the date of the first stable p-Creatinine measurement in the new stage, where “stable” was defined as a measurement performed out of hospital/outpatient (preferred) or at discharge. For terminally ill patients, we registered the last p-Creatinine measurement before terminal hospitalization. Loss of renal unit was defined as a kidney functioning at less than 10% of the total renal function based on a radioisotope renography scan.
The primary outcome of the study was development of renal insufficiency defined as the loss of renal function to CKD stage G3b or worse (eGFR<45 mL/min). This was selected as a clinically relevant threshold where patients are no longer eligible for cisplatin-based chemotherapy. Secondary outcomes were all-cause mortality of patients with and without renal insufficiency, as well as loss of renal function within specific patient groups.

Reverse Kaplan-Meier was used to calculate median follow-up for patients alive. Chi-squared test was used to test the significance of difference in population proportions of CKD stages at the time of RC versus five years postoperatively. To assess the risk of postoperative renal insufficiency, the cumulative incidence of renal function decline was plotted with death before loss of renal function as a competing risk. Renal function decline was defined as a drop from CKD-stage 3a or better preoperatively to CKD-stage G3b or worse postoperatively. Kaplan-Meier was applied to determine the overall survival probability. The cumulative incidence of death was plotted to compare mortality of patients with and without development of renal insufficiency.

The association with loss of renal function to G3b or worse was examined for: age at time of surgery, preoperative chronic hypertension, preoperative diabetes mellitus, preoperative CKD stage, prior pelvic radiation therapy, urinary diversion type, and postoperative renal catheterization. To avoid overfitting of data, urinary diversion type was excluded from the multivariate analysis, as this variable is highly influenced by patient selection, and postoperative renal catheterization was excluded, as this variable could cause immortality bias. Multivariate analyses were carried out using Cause-specific Cox Proportional Hazards Model. The proportional hazards assumption was tested.
for the model using Schoenfeld residuals and censuring for the competing event, i.e. death before loss of renal function. Any disproportionality was resolved by stratification.

Statistical analyses were performed using IBM SPSS Statistics version 25.0.0.2 (IBM, Armonk, NY, USA) and RStudio version 1.2.5001 (R Foundation for Statistical Computing, Vienna, Austria). Ninety-five percent confidence intervals (95% CI) were used, and p-values below 0.05 were considered statistically significant.

This study was approved by the Danish Patient Safety Authority (3-3013-2590/1).
Results

A total of 670 patients were included into this study (Supplementary Figure 1). The median follow-up was 6.2 years (interquartile range 4.0-8.4). Clinicopathological characteristics are shown in Table 1. A total of 537 patients (80.1%) received an ileal conduit urinary diversion, 76 (11.3%) an orthotopic neobladder, 37 (5.5%) a continent cutaneous reservoir, and the remaining 20 (3.0%) received a ureterocutaneostomy or permanent nephrostomy. Of 610 patients with a preoperative eGFR≥45, 110 patients (18%) dropped to G3b within the follow-up period. In the same group, 47 patients (8%) dropped to G4, and 15 patients (3%) dropped to G5 (end-stage renal failure). A total of 7% (43 of 584 patients) lost a renal unit within the follow-up period, with 42% of these (18 of 43 patients) experiencing development of renal insufficiency. Within the follow-up period, 135 patients (20%) required renal catherization.

Figure 1 shows the overall distribution of renal function from the time of RC to five years postoperatively, stratified by CKD stages. Patients were removed from the analysis after their last measured s-Creatinine, resulting in 670 patients included at the time of RC and 250 patients left at five years. The figure is dynamic and gives an overview of the general changes in eGFR after RC. At the time of RC, 77% of patients had normal renal function (G1 and G2), and 8.9% of patients had renal insufficiency (≥G3b). Five years postoperatively, 67% of patients had a normal renal function and 19% of patients had renal insufficiency, with 1.2% having end-stage renal failure (G5), a significant difference (p-value<0.001) in the proportion compared to at the time of RC.
Cumulative incidence of renal function decline was 6.2% (95% CI=4.3-8.2), 17% (95% CI=14-20) and 27% (95% CI=21-33) for one, five, and ten years postoperatively, respectively. In univariate analysis, preoperative CKD stage, CCI, chronic hypertension, and diabetes mellitus were significantly associated with development of renal insufficiency during follow-up (Supplementary Table 1). The risk of renal function decline and its association with preoperative eGFR, CCI, hypertension, and diabetes is depicted in Figure 2 (A-D). All factors were associated with the risk of losing renal function during follow-up.

Overall survival probability was 90% (95% CI=87-92), 66% (95% CI=62-70), and 51% (95% CI=45-57) after one, five and ten years, respectively. Figure 2E and F shows the absolute risk of death stratified by the presence of renal function decline for all patients and recurrence-free patients, respectively. When eliminating recurrence, the effect of renal function decline on overall mortality was present in univariate analysis, although statistically insignificant (p-value=0.1). The five-year absolute risk of death for patients with loss of renal function was 17.2% (95% CI=7.9-26.4) and 10.3% (95% CI=6.8-13.8) for patients without loss of renal function.

In multivariable analysis, diabetes, preoperative CKD, and prior pelvic radiation therapy were all independently associated with the loss of renal function following RC (Table 2). Perioperative age and hypertension were not independently associated with the outcome. The test for proportional hazards assumption produced a successful, non-significant global test; however, disproportionality was found for preoperative hypertension, which, when stratified, produced almost identical hazards ratio estimates for the other variables (Supplementary Table 2). Additional univariate and multivariate analyses are outlined in Supplementary Table 1. No associations were found between
loss of renal function and gender, preoperative chemotherapy, BMI, CCI, or pT stage. The univariate analysis showed no impact of type of urinary diversion on loss of renal function, but multivariate analysis showed an increased risk for patients with continent diversions (HR=2.3, 95% CI=1.4-3.8, p-value<0.001) compared to incontinent types. Postoperative renal catheterization was also found to have a significant impact on loss of renal function in multivariate analysis (HR=5.4, 95% CI=3.6-7.9, p-value<0.001).
Discussion

In this study we were able to demonstrate that BC patients have a significant risk of developing renal insufficiency after RC. One in six patients develops renal insufficiency within five years. We identified diabetes, pre-existing CKD and previous radiation therapy as preoperative factors associated with loss of renal function. Furthermore, continent urinary diversion types and development of ureteral stricture was also associated with a greater loss of renal function postoperatively. These factors should be considered when counselling patients prior to RC, as well as during follow-up.

Several other studies have described renal function outcomes following RC, but direct comparison between studies is difficult. First, the definition of loss of renal function differs. Some previous studies have defined the loss of renal function by a decrease of a certain number of eGFR units.\textsuperscript{7,12,14} One study found a renal function decline-free survival probability (eGFR not decreasing 10 mL/min or more) of around 50\% after five years and less than 30\% after ten years.\textsuperscript{14} Another study defined renal loss as a drop of a certain percentage of eGFR, and found a renal function decline-free survival probability (eGFR not decreasing by 25\% or more) of around 67\% after five years and 64\% after ten years.\textsuperscript{11} The definition of loss of renal function by a decrease of a certain number of eGFR units can potentially cause an overestimation of the number of patients with clinically relevant renal function decline. A study with 72,521 healthy individuals found that the rate of eGFR decline is significantly faster for persons with higher baseline eGFR compared to individuals with a lower baseline eGFR.\textsuperscript{15} For example, patients with an eGFR drop from 95 to 85 mL/min will neither have any clinical signs of renal function decline nor will it be as clinically significant as an eGFR drop from 45 to 35 mL/min. We chose to define changes in the renal
function by the recognized CKD stage classification. According to the KDIGO guidelines, the rate of hospitalization, cardiovascular events, and death substantially increase for patients with eGFR<45 mL/min and in our analysis one third of the patients alive ten years after RC were in G3b or worse.\textsuperscript{13}

Even studies using similar outcome measures are heterogeneous in cohort demographics, length and rigor of follow-up, and inclusion criteria. In a study from 2019, 48\% of patients were in CKD G3-G5 at the time of RC, compared to 23\% of our patient population.\textsuperscript{6} Another study reported a cohort in which 25\% had CKD G3-G5 before RC; however, they excluded patients with follow-up shorter than ten years, an exclusion of 74\% of the cohort, which may have caused selection bias towards patients with better health and low risk of recurrence.\textsuperscript{12}

One of the strengths of this study is the method of eGFR collection. Previous studies have either collected monthly or yearly creatinine measurements and directly used these in their analyses, or they have collected all creatinine measurements and used medians.\textsuperscript{7-10,14} Creatinine levels are highly influenced by urinary tract infections, temporary or permanent obstruction of the urinary tract, hydration and changes in muscle mass. Therefore, using all creatinine measurement or ones at pre-defined time points may result in incorrect estimates of the renal function. We sought to mitigate this issue by only using out of hospital/outpatient (preferred) or discharge measurements, and by not including measurements from terminally ill patients.
Another strength of this study is the high level of granularity in the Danish national EMR. All patient data, including diagnoses, creatinine measurements, prescribed medicine, hospitalizations, and deaths from all hospitals nationally are collected in the EMR, resulting in minimal missing data.

Analyses in this study present diabetes, lower preoperative renal function, and prior pelvic radiation therapy as independent preoperative risk factors for the development of renal insufficiency. Previous studies investigating risk factors for renal function decline after RC have found contradictory results. A large clinic series found age, lower preoperative renal function, and chronic hypertension to be significantly associated with loss of renal function, but no association with diabetes mellitus.\textsuperscript{7,14} In two smaller cohorts, one study found no association between loss of renal function and age, preoperative renal function, chronic hypertension or diabetes mellitus, and the other found both diabetes mellitus and chronic hypertension to be significantly associated with loss of renal function for ileal conduit patients.\textsuperscript{11,12} These diverging results may be a result of varying definitions of the primary outcome and tested variables.

It should be emphasized that peri- and postoperative factors may also play a major role in development of renal deterioration, such as urinary diversion type, development of ureteral stricture, recurrent urinary tract infections, and nephrotoxic chemotherapy in patients with recurrent cancer. The design chosen for this particular study is suboptimal for examining postoperative causes of renal deterioration. The lack of pre-defined time-specific creatinine measurements complicates the potential “cause and effect” relationship between a postoperative cause (i.e. ureteral stricture) and the postoperative effect (i.e. renal deterioration), as both events can have happened at any point
during the follow-up period. This could cause immortality bias, and should be taken into consideration when interpreting the results.

In investigating overall mortality, the lack of serial eGFR registrations may have underestimated the effect of renal function decline. For this analysis, 30-day, 6-month, and 1-year registrations may have been more appropriate. Furthermore, a lower eGFR threshold for defining renal function decline would most likely present a stronger effect on mortality as CKD stage G3b does not necessarily pose a high risk of dying. When examining the effect of renal function decline on overall mortality, BC recurrence is a major confounder, as it is the primary cause of death within the first two years after RC.\textsuperscript{2} The result presented in Figure 2F, which eliminates recurrence as a confounder, could indicate a potential statistically significant effect in a larger population size. The lack thereof may also be the result of effective treatment of CKD or other causes of death confounding the effect. We recommend further studies be produced to investigate the consequences of postoperative renal insufficiency in RC patients.

Our study is limited by its retrospective, non-randomized design. Not all patients were followed up with the recommended yearly creatinine measurements and/or renography scans throughout their follow-up time.\textsuperscript{16} This may have introduced selection bias, as patients with fewer hospitalizations and creatinine measurements are likely to have a higher average renal function.
Another limitation may be found in the estimation of GFR. According to the KDIGO Clinical guidelines, the golden standard for GFR measurement is urinary inulin clearance. However, studies have shown that imprecisions in current eGFR equations are partly caused by the random error in measured filtration rate, and for detecting and monitoring CKD, eGFR is an adequate and less costly alternative to golden standard measurements.
Conclusion

We retrospectively assessed long-term renal function in 670 bladder cancer patients who underwent radical cystectomy between 2009 and 2019. A substantial number of patients experienced a clinically significant loss of renal function, whereby the highest risk of postoperative renal insufficiency was recorded in patients with pre-existing diabetes mellitus, prior pelvic radiation therapy, lower preoperative eGFR, and a continent urinary diversion, as well as in patients who developed ureteral stricture. Acknowledging known limitations, the recent study adds important knowledge to the field of postoperative complications after RC. The study stresses the need for a multidisciplinary approach to CKD in a group of patients, whom are currently followed up routinely by urologists at our institution. A greater focus on patient involvement and education on not only their cancer diagnosis, but also the consequences of their cystectomy, especially for patients with pre-existing risk factors, may be beneficial for better health awareness and earlier diagnosis of long-term surgical complications. Further studies are needed to establish patient-specific surveillance programs and clarify the effect of early medical or surgical interventions to avoid loss of renal function following RC.
Declaration of Competing Interest

None.
1. Witjes, J. A. et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. *Eur. Urol.* **79**, 82–104 (2021).

2. Stein, J. P. et al. Radical Cystectomy in the Treatment of Invasive Bladder Cancer: Long-Term Results in 1,054 Patients. *J. Clin. Oncol.* **19**, 666–675 (2001).

3. Maibom, S. L. et al. Morbidity and Days Alive and Out of Hospital Within 90 Days Following Radical Cystectomy for Bladder Cancer. *Eur. Urol. Open Sci.* **28**, 1–8 (2021).

4. Lawrentschuk, N. et al. Prevention and Management of Complications Following Radical Cystectomy for Bladder Cancer. *Eur. Urol.* **57**, 983–1001 (2010).

5. Go, A. S. et al. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *N. Engl. J. Med.* **351**, 1296–1305 (2004).

6. Miyake, M. et al. Long-term Changes in Renal Function, Blood Electrolyte Levels, and Nutritional Indices After Radical Cystectomy and Ileal Conduit in Patients with Bladder Cancer. *Urol. Oncol.* **16**, 145–151 (2019).

7. Gershman, B. et al. Comparative impact of continent and incontinent urinary diversion on long-term renal function after radical cystectomy in patients with preoperative chronic kidney disease 2 and chronic kidney disease 3a. *Int. J. Urol.* **22**, 651–656 (2015).

8. Rouanne, M. et al. Trends in Renal Function After Radical Cystectomy and Ileal Conduit Diversion: New Insights Regarding Estimated Glomerular Filtration Rate Variations. *Clin. Genitourin. Cancer* **13**, e139–e144 (2015).

9. Yu, J. et al. Comparison of a Significant Decline in the Glomerular Filtration Rate between Ileal Conduit and Ileal Neobladder Urinary Diversions after Radical Cystectomy: A Propensity Score-Matched Analysis. *J. Clin. Med.* **9**, 2236 (2020).
10. Faraj, K. S. *et al.* The effect of urinary diversion on long-term kidney function after
cystectomy. *Urol. Oncol.* **38**, 796.e15-796.e21 (2020).

11. Osawa, T. *et al.* Long-term Renal Function Outcomes in Bladder Cancer After Radical
Cystectomy. *Urol. Oncol.* **10**, 784–789 (2013).

12. Jin, X. D. *et al.* Long-term Renal Function After Urinary Diversion by Ileal Conduit or
Orthotopic Ileal Bladder Substitution. *Eur. Urol.* **61**, 491–497 (2012).

13. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012
Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.
*Kidney Int.* **3**, 1–150 (2013).

14. Eisenberg, M. S. *et al.* Long-Term Renal Function Outcomes after Radical Cystectomy. *J.
Urol.* **191**, 619–625 (2014).

15. Baba, M. *et al.* Longitudinal Study of the Decline in Renal Function in Healthy Subjects.
*PLoS One* **10**, 1–18 (2015).

16. DaBlaCa Danish Bladder Cancer Group. Behandling og opfølgning af muskelinvasiv
blærekraft. 1–33 (2020).

17. Stevens, L. A. *et al.* Assessing Kidney Function — Measured and Estimated Glomerular
Filtration Rate. *N. Engl. J. Med.* **354**, 2473–2483 (2006).

18. Kwong, Y. T. *et al.* Imprecision of Urinary Iothalamate Clearance as a Gold-Standard
Measure of GFR Decreases the Diagnostic Accuracy of Kidney Function Estimating
Equations. *Am. J. Kidney Dis.* **56**, 39–49 (2010).
Figure 1: CKD stage distribution of the patient population from time of RC to five years postoperatively. Patients were included in the analysis until their most recent creatinine measurement before death or end of follow-up. CKD = chronic kidney disease, RC = radical cystectomy.
Figure 2: Cumulative incidence of renal function loss stratified according to (A) preoperative CKD-stage, (B) preoperative CCI, (C) preoperative chronic hypertension, and (D) preoperative diabetes mellitus, and cumulative incidence of death stratified according to loss of renal function for (E) all patients and (F) recurrence-free patients. CKD = chronic kidney disease, CCI = Charlson Comorbidity Index.
Table 1. Clinicopathological patient characteristics. IQR = interquartile range, eGFR = estimated glomerular filtration rate, CKD = chronic kidney disease, TURB = transurethral resection of bladder, RC = radical cystectomy, renal catheterization including nephrostomy and ureteral stent.

| Characteristic                                                                 | No. (%) or Median (IQR) |
|-------------------------------------------------------------------------------|-------------------------|
| Number of patients                                                            | 670 (100)               |
| Gender                                                                        |                         |
| Male                                                                          | 500 (75)                |
| Female                                                                        | 170 (25)                |
| Age at cystectomy                                                             | 68 (61-72)              |
| Preoperative Body Mass Index *                                                | 22.5 (23-29)            |
| Smoking status                                                                |                         |
| Never                                                                         | 113 (17)                |
| Prior use                                                                     | 299 (45)                |
| Active at time of surgery                                                     | 258 (39)                |
| Preoperative Charlson Comorbidity Index                                       |                         |
| CCI 0-1                                                                       | 473 (71)                |
| CCI 2-5                                                                       | 197 (29)                |
| Preoperative chronic hypertension                                            |                         |
| Preoperative diabetes mellitus                                                |                         |
| Preoperative chemotherapy                                                     |                         |
| Prior pelvic radiation therapy                                                |                         |
| Preoperative renal catheterization                                            |                         |
| Preoperative eGFR in ml/min per 1.73m²                                        |                         |
| Preoperative CKD stage                                                        |                         |
| G1 (eGFR ≥ 90 mL/min)                                                         | 159 (24)                |
| G2 (eGFR 60-89 mL/min)                                                        | 357 (53)                |
| G3a (eGFR 45-59 mL/min)                                                       | 94 (14)                 |
| G3b (eGFR 30-44 mL/min)                                                       | 49 (7.3)                |
| G4 (eGFR 15-29 mL/min)                                                        | 11 (1.6)                |
| G5 (eGFR <15 mL/min)                                                          | 0 (0.0)                 |
| Urinary diversion type                                                        |                         |
| Ileal conduit                                                                 | 537 (80)                |
| Orthotopic neobladder                                                         | 76 (11)                 |
| Continent cutaneous reservoir                                                 | 37 (5.5)                |
| Other                                                                         | 20 (3.0)                |
| pT stage (highest of preoperative TURB and RC) †                              |                         |
| pTa/is/1                                                                      | 215 (32)                |
| pT2                                                                           | 242 (36)                |
| pT3/4                                                                         | 211 (32)                |
| Postoperative loss of renal unit ‡                                            | 43 (7.4)                |
| Postoperative renal catheterization                                           | 135 (20)                |
| Postoperative renal function §                                                |                         |
| Loss of renal function to G3b                                                 | 110 (18)                |
| Loss of renal function to G4                                                  | 47 (7.7)                |
| Loss of renal function to G5 | 15 | (2.5) |
|-----------------------------|--|--|
| * Out of 600 patients       |   |     |
| † Out of 668 patients       |   |     |
| ‡ Out of 584 patients       |   |     |
| § Out of 610 patients       |   |     |
Table 2: Multivariate cause specific Cox proportional hazard analysis for variables association with loss of renal function to CKD stage G3b. CI = confidence interval, CKD= chronic kidney disease.

| Variable                                | Hazard ratio (95% CI) | P-value |
|-----------------------------------------|-----------------------|---------|
| Age at cystectomy (increase by 2 years) | 1.0 (0.97-1.1)        | 0.25    |
| Preoperative chronic hypertension       | 1.3 (0.87-2.0)        | 0.19    |
| Preoperative diabetes mellitus          | 2.5 (1.6-4.1)         | <0.001  |
| Preoperative CKD stage                  |                       |         |
| G1 (ref)                                | -                     | -       |
| G2                                      | 2.6 (1.4-4.9)         | 0.003   |
| G3a                                     | 6.8 (3.2-14)          | <0.001  |
| Prior pelvic radiation therapy          | 2.3 (1.1-4.7)         | 0.02    |