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ORIGINAL ARTICLE

The effect of urinary diversion on renal function after cystectomy for bladder cancer: comparison between ileal conduit, orthotopic ileal neobladder, and heterotopic ileocecal pouch

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Abstract

Purpose To explore the impact of ileal conduit (IC), orthotopic ileal neobladder, and MAINZ Pouch I on renal function (RF) over time.

Methods We performed a retrospective, cohort study including consecutive patients who underwent open radical cystectomy due to bladder cancer from November 2013 to June 2022. RF deterioration was calculated based on the estimated glomerular filtration rate (eGFR) through the CKD-EPI creatinine equation. A linear mixed-effects model was constructed, adjusting for multiple risk factors. The probability of achieving an eGFR reduction greater than 25% compared to baseline among different urinary diversion techniques was assessed using a Kaplan–Meier curve.

Results Overall, 107 patients received IC, 28 neobladder, and 20 MAINZ Pouch I. Those receiving IC were older and displayed more comorbidities. At follow-up, eGFR was lower by 0.09 mL/min/1.73m^2 (confidence interval − 5.87 to 5.69, $p=0.975$) in patients receiving neobladder compared to those receiving IC. Similarly, eGFR was higher by 4.64 mL/min/1.73m^2 (confidence interval − 1.57 to 10.85, $p=0.143$) in patients receiving pouch compared to those receiving IC. Accordingly, patients with higher preoperative eGFR ($p<0.001$), lower age ($p=0.048$), non-T4 histological tumor ($p=0.027$) and absence of septicemia at follow-up ($p=0.002$) presented higher eGFR values at follow-up. The three UD techniques did not differ significantly in the time-to-event analysis (log-rank test = 0.29).

Conclusions A substantial proportion of patients undergoing urinary diversion with IC, orthotopic ileal neobladder, or MAINZ Pouch I develop RF deterioration at follow-up. No significant differences were observed among the three UD techniques in terms of eGFR decline in the long-term.

Keywords Bladder cancer · Urothelial cancer · Renal function · Cystectomy

Introduction

Urinary diversion (UD) after radical cystectomy (RC) for bladder cancer is typically classified into incontinent and continent techniques. Among incontinent techniques, ileal conduit (IC) is considered the commonest UD for patients with no upper urinary tract cancer. Among continent techniques, neobladder is most often preferred as it offers an orthotopic bladder substitution. Alternatively, cutaneous techniques such as a catheterizing pouch may also be discussed [1]. Open RC remains the gold standard of treatment, even if adoption of robot-assisted RC is rapidly increasing [2]. Compared to neobladder and continent catheterizing pouch, IC is the gold standard due to its well-known results and lower complication rates. Additionally, about 25% of all patients undergoing cystectomy are not eligible for a continent UD [3].

Among the different contraindications for the selection of a continent UD, an estimated glomerular filtration rate (eGFR) of less than 40 ml/min/1.73 m^2 is considered one of the most important, as it may lead to hyperchloremic metabolic acidosis. Urine storage in the bowel mucosa results in both reabsorption of urea, potassium, and chloride, and in excretion of sodium and bicarbonate, leading, in turn, to an increased acid load that must be processed by the kidneys [4]. It should be highlighted that compromised renal

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function (RF) is associated with worse survival outcomes [5]. Accumulating evidence supports that, in most cases, patients undergoing RC develop RF deterioration in the long-term [6]. The etiology of this deterioration seems to be multifactorial. Patient's preoperative RF, age, comorbidities, oncological status, potential adjuvant treatments required, as well as short- and long-term postoperative complications such as infections, strictures, and stones are recognized independent risk factors for RF deterioration [7, 8].

Still, available literature suggests, with a low level of evidence, that the choice of UD performed is not independently associated with decreased RF. However, this has been debated [9, 10]. Based on the previous notion, existing studies have not assessed the effect of the continent catheterizing heterotopic ileocecal pouch on RF. Moreover, to facilitate statistical analyses and data interpretation, existing studies have classified different techniques into continent and incontinent and, therefore, did not assess the exact effect of each UD on RF. In this context, we performed a cohort study aiming to assess the impact of IC, orthotopic ileal neobladder, and mixed augmentation ileum and cecum (MAINZ) Pouch I on RF over time.

Methods

Study design and selection criteria

We performed this retrospective, single-center, cohort study at the Department of Urology, Martha-Maria Hospital, Nuremberg, Germany. We followed the Declaration of Helsinki principles, in lieu of a formal ethics committee approval and report our findings based on the STROBE statement for cohort studies [11].

We retrospectively searched the electronic health record database of our department for consecutive adult patients (> 18 years old) who underwent open RC with any UD due to bladder cancer between November 2013 (month electronic database launch) and June 2022. We excluded patients undergoing prior or concomitant nephrectomy or nephroureterectomy, patients receiving bilateral ureterocutaneostomy for UD, patients with eGFR lower than 40 ml/min/1.73m^2 at baseline (receiving IC in our department), patients that died within three months after the operation, as well as those with no follow-up data.

Surgical technique

All patients underwent open RC using standard techniques. For the IC diversion, an ileal segment, approximately 12 cm long, was isolated about 20 cm proximal to the ileocecal valve. The ureters were spatulated and anastomosed to the proximal end of the ileal segment in an end-to-end fashion based on the Wallace technique [12]. For the orthotopic ileal neobladder diversion, an ileal segment, approximately 70 cm long, was isolated about 20 cm proximal to the ileocecal valve. The ileal segment was then arranged in a W-shape, its limbs were sutured to one another, and the urethral anastomosis was performed. Subsequently, the ureters were implanted into the neobladder at a convenient site, following the principles of the Hautmann technique [13]. For the catheterizing MAINZ pouch I, segments from the cecum, ascending colon, and terminal ileum were isolated. These segments were spatulated and sutured to create the catheterizing pouch, and the ureters were anastomosed into the apex of the pouch. The continent outlet was created from the appendix or the terminal ileum. If the appendix could not be used as the continence outlet, an ileum intussusception nipple was constructed following the principles of the MAINZ pouch I technique [14]. For all three techniques, we used an antirefluxive implantation of the ureters.

Patient follow-up and data collection

All patients were assessed regularly either in the outpatient clinic of our department or externally by their practicing urologist based on the recommended follow-up protocol for bladder cancer [15]. Data on baseline patient characteristics, oncological status, perioperative outcomes, disease progression, short- and long-term postoperative complications, as well as creatinine values, were retrieved. The eGFR in ml/min/1.73m^2 was calculated based on the CKD-EPI creatinine equation for all timepoints [16].

Outcomes

The primary outcome of our study was to compare the deterioration of RF over time after UD by IC, orthotopic ileal neobladder and MAINZ Pouch I. Secondary outcomes included: (i) the time to achieve a reduction in the eGFR greater than 25% compared to baseline after IC, orthotopic ileal neobladder and MAINZ pouch I; (ii) the number of patients developing chronic kidney disease stage 4 or 5 at follow-up with the different UD techniques; (iii) the effect of baseline, perioperative and postoperative characteristics on RF deterioration.

Statistical analysis

All categorical variables were calculated as frequencies with proportions, and the corresponding comparisons among the three groups were performed applying the Chi-squared (χ^2) test. All continuous variables were calculated as mean ± standard deviation (SD) or median with interquartile range (IQR), and the corresponding comparisons were performed applying the ANOVA test. To compare the

deterioration of RF over time after UD by IC, orthotopic ileal neobladder, and MAINZ pouch I, a linear mixed-effects model was constructed, adjusting for preoperative eGFR, duration of follow-up, patients' age at surgery, Charlson comorbidity index, tumor status, adjuvant oncological treatment, hypertension, diabetes, septicemia, reoperation due to urinary diversion and urinary tract obstruction. The confidence intervals (CIs) of this model were also estimated. The probability of achieving an eGFR reduction greater than 25% compared to baseline after different UD techniques was assessed using a Kaplan–Meier curve. All statistical analyses were performed with the R software, and two-sided p values ≤ 0.05 were considered statistically significant.

Results

Baseline and perioperative characteristics

We included a total of 155 patients undergoing RC for bladder cancer. Their mean age was 70.3 ± 10.4 years, mean BMI 27.4 ± 4.2 kg/m^2, and mean Charlson comorbidity index 6.6 ± 2.5. A total of 107 (69%) patients were male, 88 (56.8%) were smokers and 117 (75.5%) were diagnosed with de novo muscle-invasive bladder cancer. Overall, 107 (69%) patients received IC for UD, 28 (18%) neobladder, and 20 (13%) MAINZ pouch I. The patient selection process is illustrated in Supplementary Material 1. Patients among the three groups presented statistically significant differences in their baseline characteristics. Those receiving IC were older and displayed more comorbidities. The three groups did not differ significantly in their oncological status. Importantly, even though the surgery after pouch or neobladder placement lasted longer ($p < 0.001$), the number and type of perioperative complications did not differ among the three UD techniques. The median follow-up of the included patients was 24 months (IQR 9–52.5). On the long-term, patients receiving MAINZ pouch I required more operations due to the pouch ($p = 0.016$) and presented more often with urinary tract obstruction ($p < 0.001$). The baseline characteristics and the postoperative complications of all included patients are depicted in Table 1.

Deterioration of RF over time

The mean preoperative eGFR of all patients was 73.9 ± 17.4 ml/min/1.73m^2. Patients undergoing UD with IC had lower preoperative eGFR values (69.8 ± 16.1) compared to neobladder (84.2 ± 16.6) and pouch (81.5 ± 17.1), $p < 0.001$. At the short-term postoperative timepoint evaluations (up to six months after surgery), patients with IC presented lower eGFR values. Still, in the long-term, the three UD techniques did not differ in terms of eGFR values. Importantly, eGFR gradually decreased, irrespective of the type of UD. The corresponding values and comparisons of unadjusted eGFR among the three UD groups are presented in Supplementary Material 2 and Fig. 1a.

Based on a linear mixed-effects model adjusting important risk factors for RF deterioration, the three UD techniques did not present any significant differences in the deterioration of RF over time. More specifically, eGFR was lower by 0.09 mL/min/1.73m^2 (CI − 5.87–5.69, $p = 0.975$) in patients receiving neobladder compared to those receiving IC. Similarly, eGFR was higher by 4.64 mL/min/1.73m^2 (CI − 1.57–10.85, $p = 0.143$) in patients receiving pouch compared to those receiving IC. Accordingly, patients with higher preoperative eGFR ($p < 0.001$), lower age ($p = 0.048$), non-T4 histological tumor ($p = 0.027$) and absence of septicemia at follow-up ($p = 0.002$) presented higher eGFR values at follow-up. The corresponding linear mixed-effects analysis can be seen in Supplementary Material 3.

Time-to-event analysis

At a median follow-up of 6 months (IQR 3–24), seven patients developed chronic kidney disease stage 4 or 5. Of them, six had received IC and one pouch ($p = 0.44$). The changes in chronic kidney disease stage from baseline to the last follow-up evaluation are presented in Fig. 1b. Overall, 33 patients displayed an eGFR reduction greater than 25% compared to baseline at their last follow-up evaluation of 24 months (IQR 12–48). Of them, 23 received IC, four neobladder, and six pouch ($p = 0.42$). Based on the Kaplan–Meier curve for the time-to-event of presenting an eGFR reduction greater than 25% compared to baseline at the last follow-up evaluation, the three UD techniques did not differ significantly (log-rank test = 0.29). The corresponding analysis can be seen in Fig. 1c.

Discussion

Our findings suggest that IC, orthotopic ileal neobladder, and MAINZ Pouch I lead to a similar degree of postoperative RF deterioration. After adjusting for important risk factors for RF deterioration, the three commonest UD techniques involving intestine did not display any significant differences in terms of short- and long-term eGFR change. Both the time-to-event analysis of eGFR reduction greater than 25% and the number of patients developing chronic kidney disease stage 4 or 5 at the follow-up did not differ among the three groups. Still, patients receiving MAINZ Pouch I require more operations due to the pouch and present more often with urinary tract obstruction. Importantly, eGFR decreased over time, irrespective of the type of UD.

Table 1 Baseline characteristics, as well as short- and long-term postoperative complications of the included patients based on the type of urinary diversion after radical cystectomy

Characteristic	Overall, $n=155$	Conduit, $n=107$	Neobladder, $n=28$	Pouch, $n=20$	p value
Age (years)	70.3 ± 10.4	74.4 ± 8.3	59.8 ± 8.0	63.1 ± 9.5	**< 0.001**
Male	107 (69.0%)	72 (67.3%)	27 (96.4%)	8 (40.0%)	**< 0.001**
CCI	6.6 ± 2.5	7.4 ± 2.3	4.7 ± 1.9	5.3 ± 2.2	**< 0.001**
BMI (kg/m^2)	27.4 ± 4.2	27.1 ± 3.9	27.9 ± 4.4	28.0 ± 5.6	0.53
Hypertension	102 (65.8%)	75 (70.1%)	13 (46.4%)	14 (70.0%)	0.058
Diabetes mellitus	34 (21.9%)	23 (21.5%)	7 (25.0%)	4 (20.0%)	0.90
Smoker	88 (56.8%)	52 (48.6%)	24 (85.7%)	12 (60.0%)	**0.002**
Prior abdominal surgery	76 (49.0%)	55 (51.4%)	11 (39.3%)	10 (50.0%)	0.52
De novo muscle-invasive tumor	117 (75.5%)	79 (73.8%)	21 (75.0%)	17 (85.0%)	0.57
T after cystectomy					0.016
Non-muscle-invasive	36 (21.3%)	21 (17.4%)	9 (32.1%)	6 (30.0%)	
2	42 (27.1%)	27 (25.2%)	11 (39.3%)	4 (20.0%)	
3	55 (35.5%)	40 (37.4%)	6 (21.4%)	9 (45.0%)	
4	22 (14.2%)	19 (17.8%)	2 (7.1%)	1 (5.0%)	
N after cystectomy					0.07
0	105 (67.7%)	64 (59.8%)	23 (82.1%)	18 (90.0%)	
1	10 (6.5%)	8 (7.5%)	1 (3.6%)	1 (5.0%)	
2	31 (20.0%)	26 (24.3%)	4 (14.3%)	1 (5.0%)	
3	9 (5.8%)	9 (8.4%)	0 (0.0%)	0 (0.0%)	
Metastasis at the time of cystectomy	11 (7.1%)	11 (10.3%)	0 (0.0%)	0 (0.0%)	0.070
Operative time (min)	304.6 ± 68.5	277.7 ± 52.2	370.0 ± 52.0	357.1 ± 75.6	**< 0.001**
Perioperative CD complications					0.24
0	48 (31.0%)	28 (26.2%)	13 (46.4%)	7 (35.0%)	
1	15 (9.7%)	10 (9.3%)	1 (3.6%)	4 (20.0%)	
2	46 (29.7%)	37 (34.6%)	5 (17.9%)	4 (20.0%)	
3	36 (23.2%)	26 (24.3%)	6 (21.4%)	4 (20.0%)	
4	10 (6.5%)	6 (5.6%)	3 (10.7%)	1 (5.0%)	
Adjuvant treatment	52 (33.5%)	33 (30.8%)	11 (39.3%)	8 (40.0%)	0.57
Surgery for hernia	26 (16.9%)	18 (17.0%)	3 (10.7%)	5 (25.0%)	0.43
Septicemia at follow-up	27 (17.5%)	19 (17.9%)	4 (14.3%)	4 (20.0%)	0.86
Reoperation due to urinary diversion	26 (16.9%)	18 (17.0%)	1 (3.6%)	7 (35.0%)	**0.016**
Urinary tract obstruction at follow-up	17 (11.0%)	8 (7.5%)	0 (0.0%)	9 (45.0%)	**< 0.001**

Values presented as mean ± standard deviation or n (%). The one-way ANOVA test was performed for comparisons among continuous variables and the χ^2 test for categorical variables

BMI body mass index, *CCI* Charlson Comorbidity Index, *CD* Clavien–Dindo

Our findings are in line with previous studies assessing the effect of different UD types on RF. Jin et al. evaluated retrospectively the changes in RF ten years after RC in 50 consecutive patients undergoing IC and in 111 undergoing orthotopic ileal neobladder. The authors concluded that a substantial proportion of both IC and neobladder patients experienced RF deterioration after ten years. Urinary tract obstruction and urinary tract infections were the leading causes of impaired long-term RF and, in patients with predisposing risk factors for chronic kidney disease such as diabetes or hypertension, long-term RF may be better after orthotopic ileal neobladder than after IC [8]. Nevertheless, the authors applied the Nesbit technique for IC and the Studer technique for neobladder, while the role of the pouch as UD on RF was not explored. Accordingly, patients undergoing RC for non-oncological reasons were also included, restricting the extrapolation of these findings.

Eisenberg et al. evaluated 1241 patients undergoing incontinent UD and 390 undergoing continent UD. The authors demonstrated that most patients after RC display RF deterioration in the long-term and, by ten years after the operation, the risk of RF deterioration was similar between incontinent and continent UD. Risk factors associated with RF deterioration included age, preoperative eGFR,

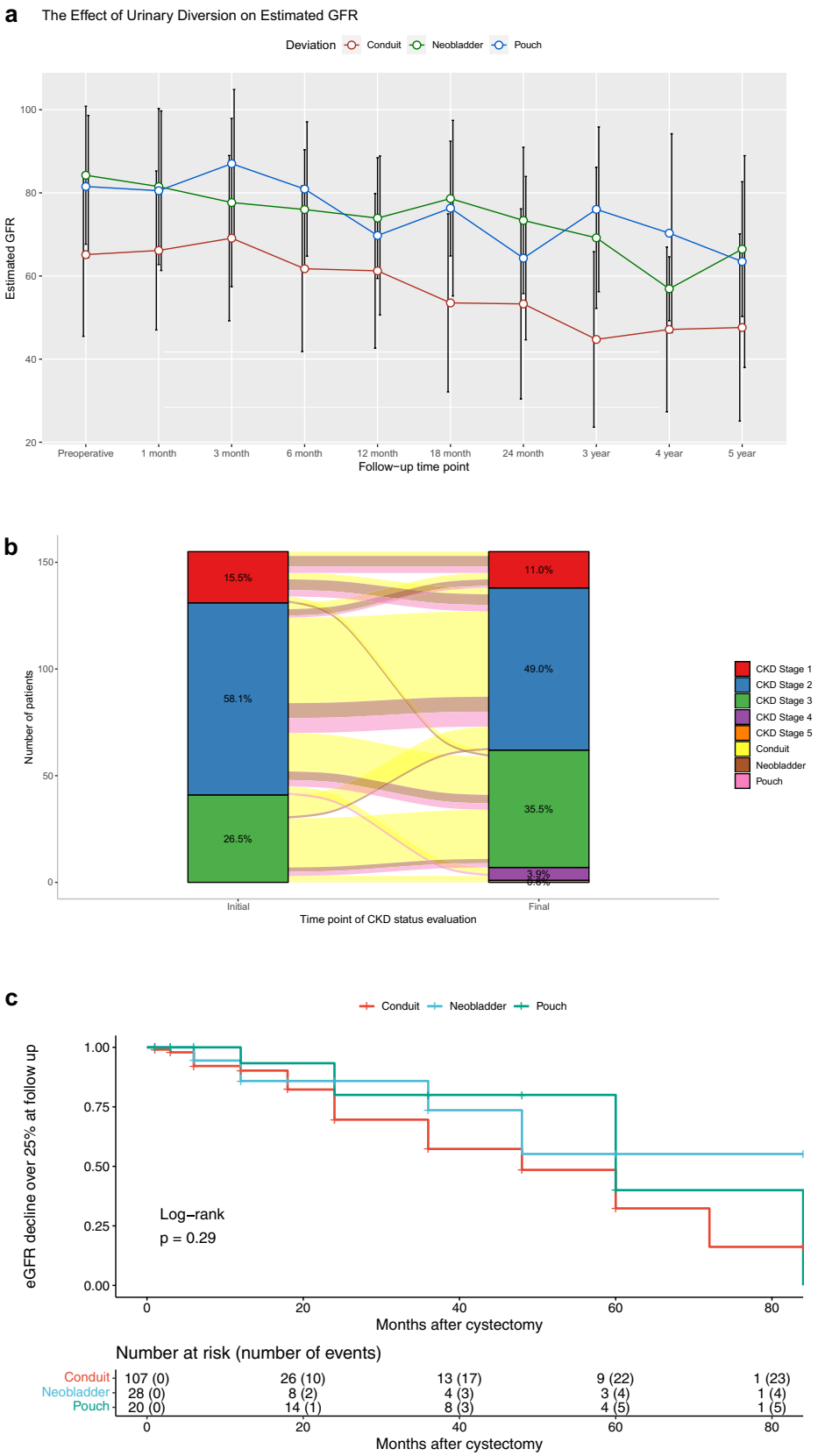

Fig. 1 **a** The effect of urinary diversion type after radical cystectomy (ileal conduit versus neobladder versus pouch) on estimated GRF at different timepoints. *GFR* estimated glomerular filtration rate. **b** The change in the CKD stage from baseline to the last follow-up evaluation based on the type of urinary diversion after radical cystectomy. *CKD* chronic kidney disease. **c** Kaplan–Meier curve for time-to-event analysis of presenting an estimated GFR reduction greater than 25% compared to baseline at the last follow-up evaluation based on the type of urinary diversion after radical cystectomy. *GFR* glomerular filtration rate

hypertension, postoperative hydronephrosis, pyelonephritis, and ureteroenteric strictures [7]. Still, given that different UD techniques were grouped into continent and incontinent categories, the authors did not evaluate the impact of each UD (IC, neobladder, and pouch) on RF.

Similarly, Gershman et al. assessed the impact of continent versus incontinent UD on long-term RF in patients with preoperative chronic kidney disease stage 2 and 3a. In these patients, the risk of eGFR deterioration over 10 years did not significantly differ after incontinent diversion versus continent UD. Additionally, the authors noted that continent UD may not lead to further eGFR decline compared to incontinent UD in patients with preoperative chronic kidney disease stage 2 and 3a. Nevertheless, their findings were mitigated by the fact that the impact of different UD techniques on RF was also not evaluated [9].

In a recent study, Faraj et al. assessed the effect of UD on long-term RF after RC. In total, 491 participants received IC, whereas 72 neobladder. Participants undergoing neobladder UD presented fewer comorbidities and higher baseline eGFR values. Compared to baseline, the included patients had a similar eGFR decrease five years after surgery (17% after neobladder and 14% after IC). After adjusting for important risk factors, the authors proposed that RF deterioration may potentially be lower over time after neobladder compared to IC. Hence, the authors attributed this observation to the better preoperative profile of patients selected for neobladder [10]. The findings of this study were also tempered by the fact that the surgical technique was not reported, and the role of the continent catheterizing pouch was not assessed. Of note, patients undergoing RC for oncological and non-oncological indications were merged for the purposes of the study.

The available literature is inconclusive about the superiority of one UD over the other for patients undergoing RC for bladder cancer. The effect of different types of UD on RF may be a deciding factor when counseling patients before surgery about the preferred UD, we provide, to our knowledge, the first study that compares three different types of UD in a holistic approach. Based on the previous notion, even though techniques involving continent catheterizing pouch are infrequently used, comparative studies assessing the role of pouch techniques on RF are lacking [17]. This study has the additional strength that RF deterioration was assessed solely for patients with bladder cancer to avoid producing clinically heterogeneous estimates, which would render their interpretation problematic. Importantly, to provide robust outcomes, RF deterioration was evaluated through multiple time-to-event and regression models.

It should be highlighted that our study was mitigated by multiple important limitations relevant to its retrospective and single-center design, as well as to its relatively small sample size of patients undergoing continent UD. Given that randomized studies on UD do not exist, patients selected for continent UD are generally healthy and present fewer comorbidities and risk factors preoperatively compared to those undergoing IC. Nevertheless, the retrospective collection of data led to the fact that creatinine was not available for all patients at all time points, while the single-center design of our study restricted the number of participants who underwent a continent UD. Of note, RF was evaluated based on eGFR from blood creatinine levels and not directly from inulin clearance. It seems that the urine storage in patients undergoing continent UD leads to creatinine reabsorption, which may result in discrepancies between eGFR and true GFR [18]. We should also acknowledge as a further limitation that patients surviving on the long-term after RC can develop both metachronous upper urinary tract carcinoma and various complications, whose effect on RF may be unpredictable and could not be adequately assessed from the present study. Importantly, even though the available literature indicates that no differences in terms of RF deterioration between open and minimally invasive radical cystectomies exist [19], we did not perform minimally invasive urinary diversion surgeries.

Conclusion

Our findings demonstrate that a substantial proportion of patients undergoing UD with IC, orthotopic ileal neobladder, or MAINZ Pouch I develop RF deterioration. No significant differences were observed among the three UD techniques in terms of eGFR decline in the long term. These findings suggest that eGFR after RC for bladder cancer should be regularly monitored and kidney-related complications should be early treated to avoid RF deterioration. Overall, patients requiring cystectomy should be counseled on both continent and incontinent UD to reach a shared decision-making.

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Availability of data and materials The raw data of the study are available after request from the authors.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This is an observational study, and no ethical approval was required.

Consent to participate and for publication Informed consent was obtained from all individual participants included in the study.

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