



Impact of urinary diversion type on urethral recurrence following radical cystectomy for bladder cancer: propensity score matched and weighted analyses of retrospective cohort

Jiwoong Yu, MD, Chung Un Lee, MD, Jae Hoon Chung, MD, PhD, Wan Song, MD, PhD, Minyong Kang, MD, PhD, Hwang Gyun Jeon, MD, PhD, Byong Chang Jeong, MD, PhD, Seong Il Seo, MD, PhD, Seong Soo Jeon, MD, PhD, Hyun Hwan Sung, MD, PhD*

Background: The absence of randomized controlled trials and the presence of inherent selection bias in existing studies have led to ongoing uncertainty regarding the impact of urinary diversion (UD) type (orthotopic UD or nonorthotopic UD) on urethral recurrence (UR) following radical cystectomy (RC) for bladder cancer. This study aimed to assess the impact of the UD types on UR after RC and to identify predictive factors associated with UR.

Materials and methods: This retrospective analysis encompassed 612 male patients who underwent RC for urothelial carcinoma of the bladder. Among them, 341 patients received nonorthotopic UD [ileal conduit (IC) or ureterocutaneostomy (UC)], whereas 271 received orthotopic neobladder (NB) between January 2012 and October 2022. To mitigate potential biases, we employed 1:1 propensity score matching (PSM) and stabilized inverse probability treatment weighting (IPTW). Kaplan–Meier analysis and log-rank tests were employed to assess UR-free survival between the IC/UC and NB groups, while multivariable Cox regression analysis was conducted to determine predictive factors for UR.

Results: Among the 612 patients included, 33 (5.4%) experienced UR. PSM yielded matched cohort comprising 412 patients, evenly distributed with 206 patients in each group (IC/UC and NB). Clinicopathological data demonstrated similarity between the two groups. Patients who underwent NB exhibited significantly superior UR-free survival in both PSM (log-rank $P = 0.033$) and IPTW cohorts (log-rank $P = 0.009$). NB reconstruction (vs. IC/UC) emerged as a substantial protective factor against UR [hazard ratio (HR) 0.283; 95% CI: 0.088–0.916; $P = 0.035$], whereas prostatic urethral involvement was identified as a significant risk factor (HR 5.328; 95% CI: 1.298–21.868; $P = 0.020$) in the PSM cohort. Additionally, in the IPTW cohort, NB reconstruction (vs. IC/UC) maintained its significance as a protective factor against UR (HR 0.336; 95% CI: 0.131–0.858; $P = 0.023$) along with neoadjuvant chemotherapy (HR 0.335; 95% CI: 0.116–0.969; $P = 0.044$), whereas prostatic urethral involvement remained a significant risk factor (HR 3.752; 95% CI: 1.484–9.488; $P = 0.005$).

Conclusions: Even after mitigating selection bias, NB reconstruction holds a protective effect against UR in male patients undergoing RC for bladder cancer.

Keywords: bladder cancer, propensity score, radical cystectomy, selection bias, urethral recurrence

Introduction

Radical cystectomy (RC) accompanied by pelvic lymph node dissection and urinary diversion (UD) is considered the optimal treatment for patients with muscle-invasive bladder cancer

(MIBC), as well as for those with high-risk recurrent nonmuscle-invasive bladder cancer (NMIBC)^[1]. Given the pan-urothelial nature of bladder cancer, the extravesical urothelium after RC, which encompasses both the upper urinary tract and urethra,

Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

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*Corresponding author. Address: Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Republic of Korea. Tel.: +822 3410 0737; fax: +822 3410 6992. E-mail: hyunhwan.sung@samsung.com (H.H. Sung).

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poses a persistent risk for cancer recurrence throughout the lifetime of the patient^[2,3].

The incidence of urethral recurrence (UR) after RC ranges from 1 to 8%^[4–8]. Several risk factors have been posited, such as pathologic T stage^[9,10], prostatic urethral involvement^[6,8,9,11,12], prostatic stromal invasion^[12], and tumor multifocality^[6,8]; however, their associations have yielded inconsistent results. A recent meta-analysis indicated that these histopathological factors may not have a significant impact on UR^[13]. Nevertheless, it is worth noting that retrospective studies and meta-analyses consistently underscore a lower UR rate in patients with orthotopic neobladders (NB) compared with those with nonorthotopic UD, such as ileal conduit (IC) or ureterocutaneostomy (UC)^[6,8–10,13–15].

These observations raise questions concerning the potential influence of inherent selection bias in previous studies, particularly within the decision-making process regarding the choice of the UD type. To address these uncertainties, we employed propensity score matched and weighted analyses to mitigate selection bias and investigate the impact of UD type on UR, while concurrently identifying predictive factors associated with UR.

Materials and methods

Study population

We accessed a prospectively maintained database to examine male patients diagnosed with high-risk recurrent NMIBC or MIBC who underwent RC at our institution between January 2012 and October 2022. The exclusion criteria encompassed: malignancies other than urothelial carcinoma (UcA) within 5 years prior to RC, RC performed for bladder cancer types other than UcA (e.g. sarcoma or adenocarcinoma), follow-up duration <3 months, previous pelvic radiation therapy, simultaneous urethrectomy during RC, and RC without UD.

The UD type was selected based on disease-related factors and involved a collaborative decision-making process involving the surgeon and patient. NB reconstruction was not considered in patients with preoperative tumor extension into the urethra, compromised renal and/or liver function, or other significant psychiatric or neurological conditions. The approach for managing positive urethral margins identified during the intraoperative frozen section analysis was at the discretion of the surgeon.

This study was approved by the Institutional Review Board of our institution (IRB File No. 2023-07-106), and the requirement for written informed consent was waived owing to the retrospective nature of the study. In addition, this study has been reported in line with the STROCSS criteria (Supplemental Digital Content 1, <http://links.lww.com/JS9/B345>)^[16].

Data collection

Relevant clinicopathological characteristics of patients, including age at surgery, BMI, smoking history, American Society of Anesthesiologists (ASA) score, surgical approach (open surgery vs. minimally invasive surgery), pathologic T and N stages, pathological features of RC specimen [presence of carcinoma in situ (CIS), prostatic urethral involvement, prostatic stromal invasion, tumor multifocality, and urethral margin status], receipt of neoadjuvant chemotherapy (NAC) or adjuvant

HIGHLIGHTS

- The lack of randomized controlled trials and the presence of selection bias in existing studies on clinical predictors of urethral recurrence (UR) after radical cystectomy for bladder cancer makes it difficult to determine the influence of urinary diversion type on UR.
- After adjusting for confounding factors through propensity score matching and stabilized inverse probability treatment weighting, patients who underwent neobladder reconstruction experienced significantly improved UR-free survival compared with those who underwent nonorthotopic diversion (ileal conduit or ureterocutaneostomy).
- Neobladder reconstruction was found to be protective against UR after radical cystectomy, while prostatic urethral involvement remained a significant risk factor.

chemotherapy, and UD type (IC/UC vs. NB), were obtained from medical records.

UR was diagnosed through endoscopy, tissue biopsy, or radiologic assessment. Data related to symptoms indicative of UR, such as hematuria, voiding symptoms, pain, discomfort, or urethral discharge, prompting further confirmatory testing for UR were collected.

Histological evaluation of RC, urethrectomy, and transurethral resection of the urethral tumor was performed following formalin fixation, paraffin embedding, and sectioning. These sections underwent meticulous review by an expert pathologist specializing in genitourinary cancer. Tumor staging and grading adhered to the 2010 TNM classification established by the American Joint Committee on Cancer and the 2004 WHO/International Society of Urologic Pathology consensus classification.

Follow-up protocol

Each patient underwent follow-up in accordance with the relevant guidelines and institutional protocols. The postoperative follow-up schedule included examinations at 1 month, followed by subsequent evaluations at 3-month to 6-month intervals within the first 2 years, annually over the ensuing 3 years, and as clinically indicated thereafter. These assessments included physical examinations, laboratory tests, cytology, and computed tomography or MRI of the chest, abdomen, and pelvis. Bone scintigraphy was performed when clinically deemed necessary. Local tumor recurrence and distant metastasis were closely monitored at each examination. To follow-up for UR, we conducted urethral washing cytology for patients with IC/UC and voided urine cytology for patients with NB. Cystoscopy and/or urethroscopy were performed according to suggestive symptoms and/or abnormal urine cytology.

Statistical analysis

Continuous variables were presented as mean $\pm$ SD and median [interquartile range (IQR)]. Categorical variables were reported as absolute numbers and percentages. Statistical comparisons of continuous variables were performed using an independent *t*-test, whereas categorical variables were analyzed using Pearson's χ^2 test or Fisher's exact test, as appropriate.

A logistic regression model was employed to assess the propensity score of each patient, with the UD type as the binary

variable. In this model, IC/UC served as the control group and NB as the treatment group. Covariates, including age (cutoff of 60 years), BMI (cutoff of 25 kg/m², the threshold for obesity in the Asia-Pacific population), smoking history (never smoker vs. prior or current smoker), ASA score, surgical approach (open surgery vs. minimally invasive surgery), pathologic T and N stages at RC, pathological features (presence of CIS, prostatic urethral involvement, prostatic stromal invasion, and tumor multifocality), and receipt of NAC or adjuvant chemotherapy, were included in the model. Propensity scores were employed using two methods to address potential selection bias and confounding factors (1): propensity score matching (PSM), and (2) stabilized inverse probability treatment weighting (IPTW). PSM was performed without replacement in a 1:1 ratio using nearest-neighbor matching, employing a caliper of 0.25 times the SD of the logit of the propensity score. The quality of the match was assessed by reviewing the distribution of propensity scores and balance of covariates after matching. In the IPTW analysis, the stabilized weight of each patient was calculated by multiplying the propensity score by the probability of receiving the actual treatment. The distribution of covariates was assessed by applying weights. In both the PSM and IPTW models, standardized mean differences of <0.1 were considered acceptable indicators of balance between the treatment groups.

The primary objective of this study was to compare UR-free survival between patients who underwent IC/UC and those who underwent NB. The comparison was carried out using Kaplan–Meier analysis with a log-rank test in two propensity score-adjusted cohorts (PSM cohort and IPTW cohort). Additionally,

multivariable Cox proportional hazards analyses were employed to identify predictive factors associated with UR. Furthermore, within the entire study cohort, a log-rank test with subsequent Holm-corrected post-hoc pairwise comparisons were performed to compare the overall survival (OS) among patients with different recurrence locations (no disease recurrence, UR, upper urinary tract recurrence, abdominal/pelvic recurrence, and distant metastasis). Patients with synchronous recurrence in both the urethra and other locations were excluded from the OS analysis. Statistical analyses were conducted using R version 4.2.3, and two-tailed *P* values <0.05 were considered statistically significant.

Results

Cohort characteristics

Of the initial cohort of 736 male patients who underwent RC, 612 met the inclusion criteria (Fig. 1). Among them, 341 underwent IC/UC and 271 underwent NB. Out of the 612 patients, 33 (5.4%) experienced UR, with 26 (7.6%) in the IC/UC group and 7 (2.6%) in the NB group. The median duration from RC to UR was 15.1 months (IQR 9.6–33.4).

Before PSM, baseline characteristics such as age, BMI, ASA score, surgical approach, pathologic T stage, presence of prostatic urethral involvement, prostatic stromal invasion, and the proportion of patients receiving NAC exhibited variations between the IC/UC and NB groups (Table 1). The median follow-up duration was 28.7 months (IQR 14.9–62.3) in the IC/UC group and 42.4 months (IQR 23.6–61.3) in the NB group.

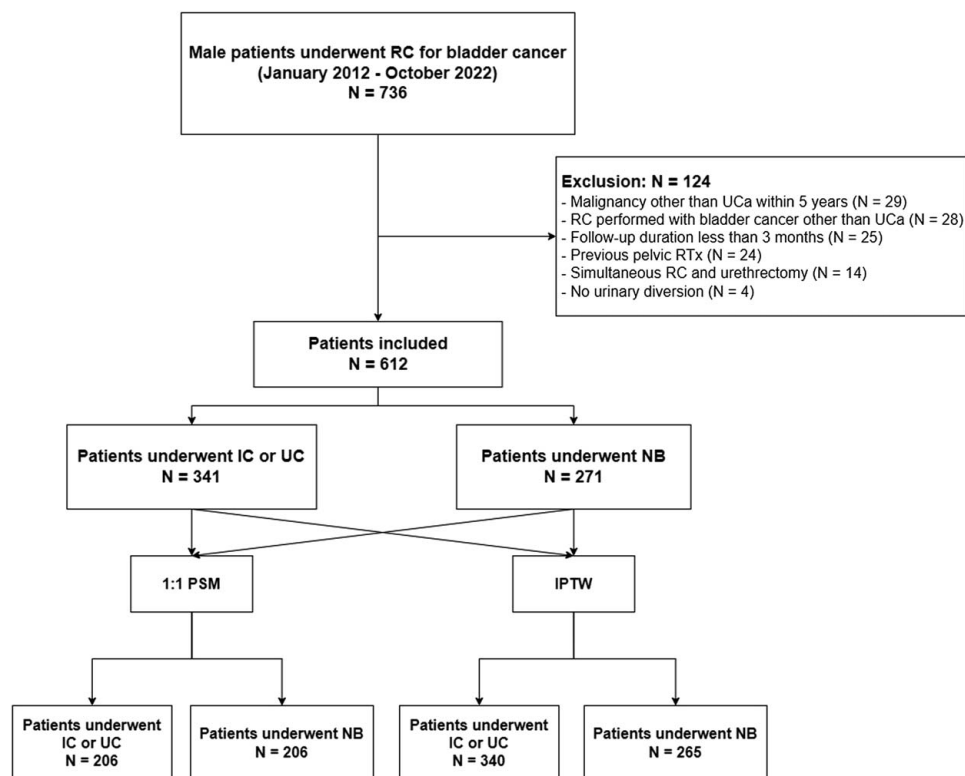


Figure 1. Flowchart depicting patient inclusion and exclusion for the analysis cohort. IC, ileal conduit; IPTW, inverse probability treatment weighting; NB, neobladder; PSM, propensity score matching; RC, radical cystectomy; RTx, radiation therapy; UC, ureterocutaneostomy; UCa, urothelial carcinoma.

Table 1
Baseline characteristics before and after propensity score matching.

UD type	Before matching			After matching		
	IC/UC (N = 341)	NB (N = 271)	P	IC/UC (N = 206)	NB (N = 206)	P
Age at surgery, years						
Mean $\pm$ SD	68.7 $\pm$ 8.7	62.3 $\pm$ 8.9	< 0.001	67.6 $\pm$ 9.3	64.0 $\pm$ 8.2	< 0.001
Median [IQR]	70.0 [63.0–75.0]	63.0 [57.5–68.0]	< 0.001	69.0 [61.0–75.0]	65.0 [60.0–69.0]	< 0.001
Age < 60 n (%)	48 (14.1)	93 (34.3)	< 0.001	46 (22.3)	49 (23.8)	0.815
Age $\geq$ 60 n (%)	293 (85.9)	178 (65.7)		160 (77.7)	157 (76.2)	
BMI, kg/m ²						
Mean $\pm$ SD	24.0 $\pm$ 2.9	24.6 $\pm$ 2.9	0.005	24.5 $\pm$ 2.7	24.4 $\pm$ 2.8	0.752
Median [IQR]	23.9 [22.2–25.9]	24.8 [22.8–26.4]	0.005	24.7 [22.8–26.2]	24.4 [22.6–26.2]	0.720
BMI < 25 n (%)	215 (63.0)	143 (52.8)	0.013	113 (54.9)	118 (57.3)	0.691
BMI $\geq$ 25 n (%)	126 (37.0)	128 (47.2)		93 (45.1)	88 (42.7)	
Smoking history, n (%)						
Never smoker	85 (24.9)	58 (21.4)	0.354	44 (21.4)	48 (23.3)	0.723
Prior/Current smoker	256 (75.1)	213 (78.6)		162 (78.6)	158 (76.7)	
ASA score, n (%)						
ASA score 1	36 (10.6)	49 (18.1)	0.011	29 (14.1)	27 (13.1)	0.886
ASA score 2–3	305 (89.4)	222 (81.9)		177 (85.9)	179 (86.9)	
Surgical approach, n (%)						
Open surgery	257 (75.4)	129 (47.6)	< 0.001	127 (61.7)	117 (56.8)	0.367
MIS	84 (24.6)	142 (52.4)		79 (38.3)	89 (43.2)	
pT-stage, n (%)						
pT0/pTis/pTa/pT1	119 (34.9)	126 (46.5)	0.004	87 (42.2)	87 (42.2)	0.870
pT2	74 (21.7)	60 (22.1)		50 (24.3)	46 (22.3)	
pT3–4	148 (43.4)	85 (31.4)		69 (33.5)	73 (35.4)	
pN-stage, n (%)						
pNx/pN0–1	275 (80.6)	235 (86.7)	0.058	183 (88.8)	178 (86.4)	0.550
pN2–3	66 (19.4)	36 (13.3)		23 (11.2)	28 (13.6)	
CIS, n (%)	137 (40.2)	117 (43.2)	0.506	91 (44.2)	91 (44.2)	1
Prostatic urethral involvement, n (%)	62 (18.2)	27 (10.0)	0.006	24 (11.7)	26 (12.6)	0.880
Prostatic stromal invasion, n (%)	61 (17.9)	25 (9.2)	0.003	19 (9.2)	23 (11.2)	0.625
Multifocal disease, n (%)	74 (21.7)	48 (17.7)	0.261	38 (18.4)	38 (18.4)	1
Pos Urethral margin ^a , n (%)	15 (4.4)	5 (1.8)	0.124	5 (2.4)	5 (2.4)	1
Neoadjuvant CTx, n (%)	106 (31.1)	106 (39.1)	0.047	73 (35.4)	81 (39.3)	0.476
Adjuvant CTx, n (%)	85 (24.9)	60 (22.1)	0.478	43 (20.9)	46 (22.3)	0.811

^aThis variable was excluded from propensity score calculations.

ASA, American Society of Anesthesiologists; CIS, carcinoma in situ; CTx, chemotherapy; IC, ileal conduit; IQR, interquartile range; MIS, minimally invasive surgery; NB, neobladder; pN, pathologic N stage; Pos, positive; pT, pathologic T stage; UC, ureterocutaneostomy; UD, urinary diversion.

After PSM, a balanced cohort of 412 patients (206 in each group: IC/UC and NB) was achieved, showing balanced distribution of all clinicopathological characteristics between the IC/UC and NB groups (Table 1). In the IPTW cohort, the IC/UC group consisted of 340 weighted patients, whereas the NB group consisted of 265 weighted patients. The distribution of propensity scores and covariate balance in both groups before and after matching is shown in the Supplemental Digital Content 1 (Supplementary Figures 1A and 1B), <http://links.lww.com/JS9/B346>. Furthermore, the absolute standardized mean differences of the variables for both the PSM and IPTW analyses were below the acceptable threshold of 0.1, as illustrated in the Supplemental Digital Content 1 (Supplementary Figures 1C and 1D), <http://links.lww.com/JS9/B346>.

Association of UD type and histopathological factors with UR

Kaplan–Meier survival analysis showed a lower incidence of UR and superior UR-free survival in the NB group than in the IC/UC group in both the PSM (log-rank $P = 0.033$; Fig. 2A) and IPTW cohorts (log-rank $P = 0.009$; Fig. 2B).

In the multivariable Cox regression analysis of the PSM cohort (Table 1A), NB reconstruction showed a significant association with lower UR risk as an independent protective factor in contrast to IC/UC [hazard ratio (HR) 0.283; 95% CI: 0.088–0.916; $P = 0.035$]. Additionally, prostatic urethral involvement was identified as a significant risk factor for UR (HR 5.328; 95% CI: 1.298–21.868; $P = 0.020$). Furthermore, in the IPTW cohort (Table 1B), NB reconstruction remained a significant protective factor against UR (HR 0.336; 95% CI: 0.131–0.858; $P = 0.023$) along with the administration of NAC (HR 0.335; 95% CI: 0.116–0.969; $P = 0.044$). Notably, prostatic urethral involvement continued to be a significant risk factor for UR (HR 3.752; 95% CI: 1.484–9.488; $P = 0.005$).

In the analysis of 89 patients with prostatic urethral involvement, out of the 27 patients with NB, two (7.4%) experienced UR, whereas among the 62 patients with IC/UC, 11 (17.7%) experienced UR (Fisher's exact test, $P = 0.329$). The univariable Cox model demonstrated that NB reconstruction in patients with prostatic urethral involvement did not increase the risk of UR (HR 0.387; 95% CI: 0.086–0.1749; $P = 0.217$).

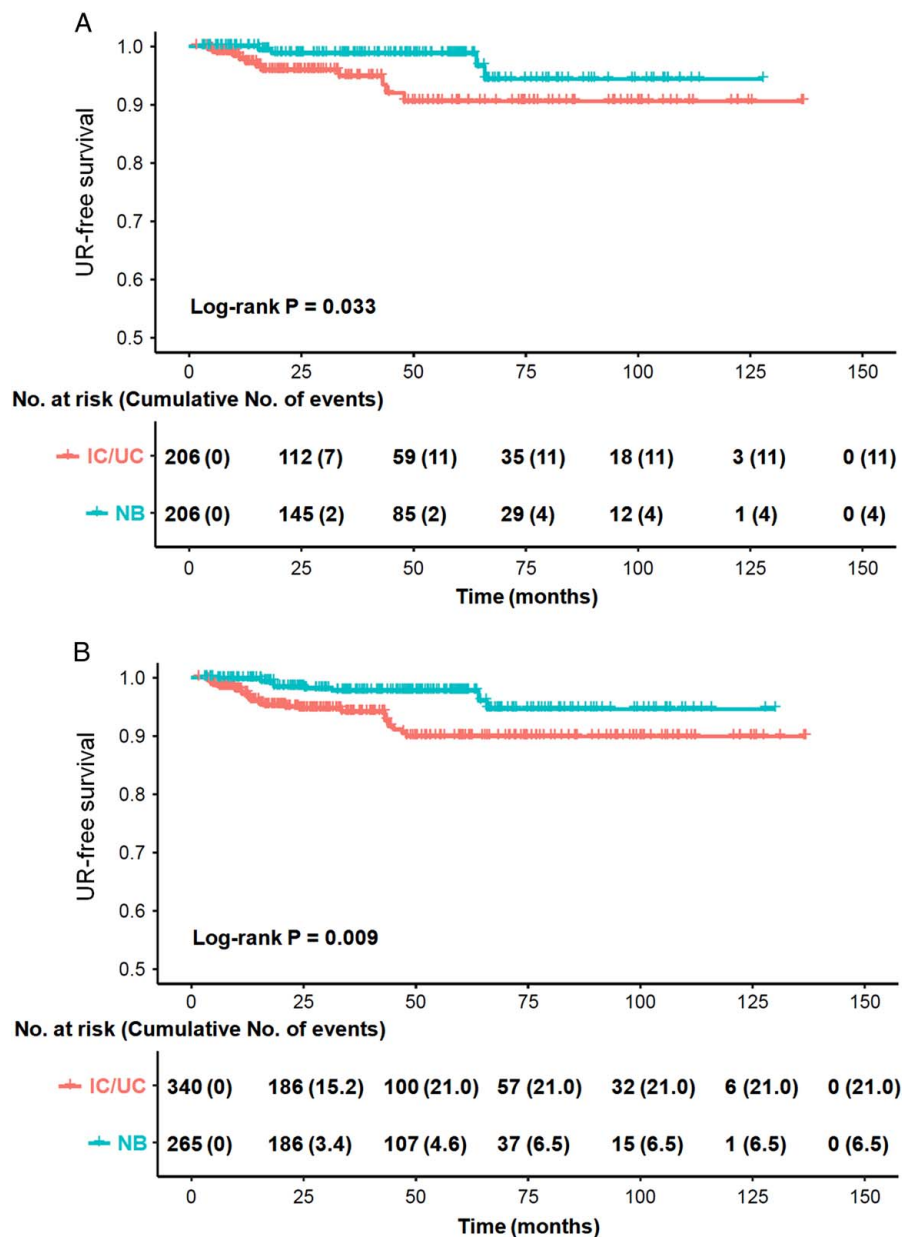


Figure 2. Kaplan–Meier survival curves depicting urethral recurrence-free survival according to the type of urinary diversion in the PSM cohort (A) and the IPTW cohort (B). IC, ileal conduit; NB, neobladder; UC, ureterocutaneostomy; UR, urethral recurrence.

Pattern of diagnosis, treatment, and prognosis of patients with UR

Among the 33 patients with UR in the entire cohort, 29 (87.9%) reported symptoms suggestive of UR. Specifically, all seven patients with UR in the NB group experienced symptoms: three reported voiding difficulty, two had hematuria, and two presented with both symptoms. Similarly, within the IC/UC group, 84.6% (22/26) of the patients with UR presented symptoms: 17 complained of urethral discharge and five of perineal pain or discomfort. No significant difference was observed in symptom presence between the IC/UC and NB groups (84.6 vs. 100%; Fisher's exact test $P = 0.555$).

Regarding UR management, 22 patients (66.7%) underwent urethrectomy, whereas 8 (24.2%) were treated with transurethral resection of the urethral tumor and/or radiation therapy. The remaining two patients (6.1%) underwent only systemic chemotherapy because of synchronous recurrences in other locations, and one patient (3.0%) was lost to follow-up after UR diagnosis. Furthermore, among the 22 patients who underwent urethrectomy, pathologic staging revealed that one patient had T0, four had Ta, five had Tis, six had T1, and six had T2 tumors. In the instance of the T0 stage found in the urethrectomy specimen, the patient initially presented with definite UCa during urethroscopy, and subsequent partial penectomy that confirmed the

UCa diagnosis. Notably, three patients underwent partial or total penectomy, and among them, one patient exhibited extension of UCa to the corpus cavernosum and tunica albuginea.

Significant differences in OS were observed among different recurrence locations, including no disease recurrence, UR, upper urinary tract recurrence, abdominal/pelvic recurrence, and distant metastasis (log-rank $P < 0.001$; Fig. 3). In the post-hoc pairwise analysis, distant recurrence was associated with a significantly poorer OS than all other recurrence sites (Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/JS9/B346>). Notably, only UR did not exhibit a statistically significant difference in OS when compared with the absence of recurrence ($P = 0.075$; Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/JS9/B346>).

Discussion

To the best of our knowledge, this study is the first to comprehensively compare the risk of UR following RC according to UD type, employing both PSM and IPTW to mitigate selection bias. Additionally, we investigated the predictive factors associated with UR, and assessed prognostic value of UR. Our analysis revealed a significantly superior UR-free survival in patients who underwent NB compared with those who underwent IC/UC. Furthermore, in both statistical methodologies, NB reconstruction consistently demonstrated a significant protective effect against UR compared with IC/UC.

In clinical practice, patients with advanced-stage bladder cancer, prostatic urethral extension, or extensive CIS frequently opt for IC/UC over NB reconstruction. Nonetheless, a consistent trend has emerged from retrospective studies and meta-analyses, revealing a reduced UR risk in patients who underwent NB compared with those who underwent IC/UC^[6,8–10,13–15]. Interpretating the relationship between UD type and UR is often hampered by inherent selection bias. However, our analysis of both propensity score matched and weighted cohorts

yielded evidence independent of potential biases. Moreover, the subgroup analysis demonstrated that NB reconstruction in patients with prostatic urethral involvement did not lead to a heightened UR risk. In a similar context, earlier research has investigated the role of preoperative urethral biopsy, and the prevailing consensus suggests that the preoperative identification of urethral involvement should automatically exclude the possibility of considering NB reconstruction^[17–20]. By potentially expanding the range of patients eligible for NB reconstruction, this study suggests an increased likelihood of aligning with patient preferences in adopting UD type, particularly in relation postsurgical urinary continence and psycho-social well-being.

In addition to the selection bias, other factors could potentially contribute to this phenomenon. Several studies have put forth hypotheses suggesting the involvement of biological mechanisms as potential rationales for this correlation. Freeman *et al.* initially suggested that this phenomenon might be attributed to the inherent resistance of the ileum, encompassing its physiological, biochemical, genetic, and immunological characteristics. These factors could potentially confer resistance to malignancy and extend this protective effect to neighboring tissues as well^[4]. In a study comparing intestinal mucosa between patients with NB and those with IC, immunostaining and staining of fragmented DNA were performed to assess proliferative and apoptotic changes^[21]. The results revealed statistically significant differences, with the ileal tissues in patients who underwent NB displaying more notable changes in proliferation and apoptosis compared with those who underwent IC^[21]. Furthermore, in a comparative study that evaluated urethral tissues obtained from patients who underwent NB and those without UD, although no differences were found in the T-cell populations, there was a significant abundance of B-cells, predominantly characterized as plasma cells, in the urethral tissues of patients who underwent NB. This finding suggests an immunogenic effect stemming from the interaction between ileal and urethral tissues, potentially leading to an enhanced local immune response against carcinogenic antigens^[22].

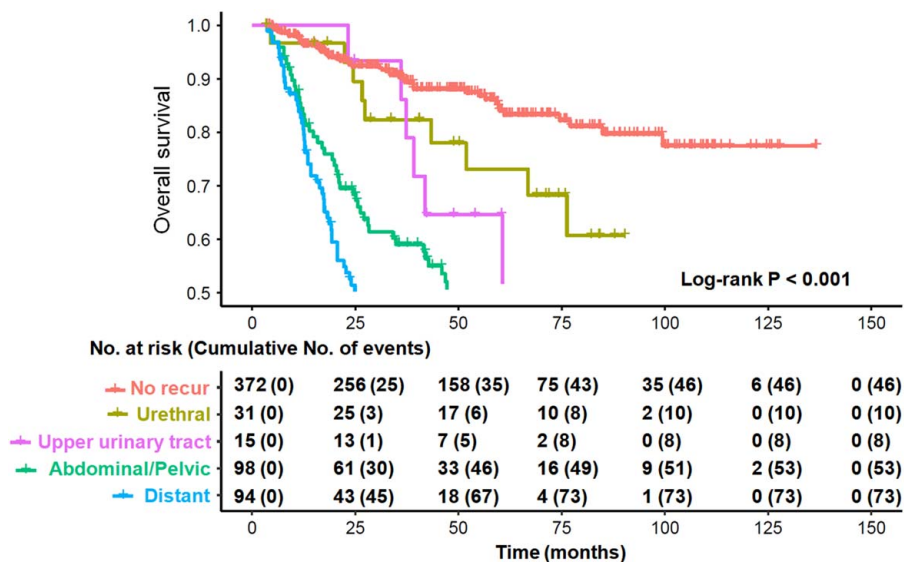


Figure 3. Kaplan–Meier survival curves illustrating overall survival according to recurrence locations in the entire cohort. *Among the 33 patients with urethral recurrence, two patients presenting with synchronous recurrences in both the urethra and other locations were excluded from this analysis.

Despite numerous studies reporting various clinical and histopathological predictors of UR following RC, a lack of consistent findings persists, contributing to the ambiguity in this field. As summarized in Table 3, previous studies have examined potential confounding factors and suggested that factors including history of NMIBC^[9], pathologic T stage^[9,10], presence of CIS^[8], prostatic urethral involvement^[6,8,9,11,12], prostatic stromal invasion^[12], tumor multifocality^[6,8], and positive urethral margin^[12] are independently associated with UR. In the present study, prostatic urethral involvement was an independent risk factor in both the matched and weighted cohorts. Notably, within the pathology reports of our institution, a distinction is made between prostatic stromal invasion and prostatic urethral involvement. Among the 86 patients with prostatic stromal invasion in our study, 38 (44.2%) displayed evidence of prostatic urethral involvement. This differentiation classifies stromal invasion into intraurethral, extravascular, and direct invasion^[23], with the implication that the intraurethral invasion pattern might be more strongly linked to UR after RC compared with the other two invasion patterns. Moreover, previous studies have indicated that there is no significant association between lymph node positivity and the risk of UR^[8,10,24]. However, guidelines and previous research have suggested that extensive lymph node metastasis (N2 or N3) is associated with poorer outcomes, particularly in terms of local recurrence, following RC with NB, leading to consideration of alternative reconstruction options for this specific patient population^[19,25]. Although our objective was to investigate the potential risk of extensive lymph node metastasis in relation to UR, we were unable to establish a significant association between extensive lymph node metastasis (N2 or N3) and an increased incidence of UR.

In the context of the final pathology following RC, a positive urethral margin was identified in a limited subset of 20 patients in our cohort, posing challenges in incorporating it into statistical models and comparative analyses. Notably, within this subset, three patients (15.0%) experienced UR. Intraoperative urethral

margin analysis is recognized as a pivotal factor in determining patient eligibility for NB reconstruction^[19,20,26]. Therefore, we speculate that these findings could be attributed to the elevated likelihood of patients with positive urethral margins at the time of surgery refraining from undergoing NB at our institution. Nevertheless, the PSM cohorts in our study exhibited a balance in terms of the proportion of patients with positive urethral margins, which was equal between the IC/UC and NB groups (5/206 in each group).

Regarding UR diagnosis and prognosis, we observed a higher rate [87.9% (29/33)] of symptom manifestation for UR diagnosis, compared with a recent study in which UR diagnosis was symptom-based in 43.8% (63/144) of patients^[8]. In cases of UR in patients undergoing NB, all seven patients exhibited symptoms such as voiding difficulty or hematuria in our study cohort. Consistent with previous research in which more than half of the patients (40/63) presented with urethral discharge^[8], 17 of 22 symptomatic patients who underwent IC/UC reported urethral discharge as the predominant complaint in our study. Additionally, earlier studies have indicated that symptomatic UR is associated with higher tumor stage and poorer prognosis than asymptomatic UR^[6,8,27]. However, within our study, the majority of patients (29/33) exhibited symptoms, which limited our ability to compare the impact of symptom manifestation on the tumor stage or prognosis. Notably, all three patients who eventually required penectomy were initially diagnosed with UR based on their symptoms. Meanwhile, despite several studies demonstrating an association between UR and poor survival^[6,8], other studies have alternatively proposed that UR may not exert a substantial impact on survival^[10,13]. It remains unclear whether poor survival associated with UR is attributable to UR alone or to concomitant metastasis to other sites. To address this, we conducted a survival analysis in which recurrence sites were stratified. The Kaplan–Meier curve indicated a potential association between UR and poorer OS compared with patients without recurrence (Fig. 3). However, further post-hoc analysis within

Table 2
Multivariable Cox proportional regression analysis for urethral recurrence-free survival in the PSM (A) and IPTW cohorts (B).

Variables	(A) PSM			(B) IPTW		
	HR	95% CI	P	HR	95% CI	P
Type of UD (NB vs. IC/UC)	0.283	0.088–0.916	0.035	0.336	0.131–0.858	0.023
Age (≥ 60 vs. <60)	0.576	0.170–1.953	0.376	0.629	0.261–1.515	0.301
BMI (≥ 25 vs. <25)	0.795	0.260–2.433	0.688	1.181	0.526–2.649	0.688
Smoking (Prior/Current vs. Never)	2.318	0.555–9.674	0.249	1.481	0.646–3.394	0.353
Surgical approach (MIS vs. Open)	0.697	0.217–2.237	0.544	0.690	0.280–1.701	0.420
ASA score (2–3 vs. 1)	1.776	0.361–8.737	0.480	3.742	0.781–17.926	0.099
Pathologic T stage						
pT0/pTis/pTa/pT1		Reference			Reference	
pT2	1.488	0.391–5.665	0.560	1.529	0.517–4.528	0.443
pT3–4	0.622	0.109–3.549	0.594	1.285	0.422–3.917	0.659
Pathologic N stage (pN2–3 vs. pNx/pN0–1)	0.550	0.054–5.566	0.612	0.309	0.067–1.429	0.133
CIS	1.921	0.555–6.653	0.303	0.905	0.390–2.100	0.816
Prostatic urethral involvement	5.328	1.298–21.868	0.020	3.752	1.484–9.488	0.005
Prostatic stromal invasion	1.084	0.229–5.119	0.919	1.831	0.644–5.205	0.256
Multifocal disease	1.656	0.430–6.373	0.463	1.313	0.548–3.144	0.541
Neoadjuvant chemotherapy (yes vs. no)	0.341	0.071–1.650	0.181	0.335	0.116–0.969	0.044
Adjuvant chemotherapy (yes vs. no)	1.963	0.421–9.150	0.390	1.043	0.419–2.596	0.928

ASA, American Society of Anesthesiologists; CIS, carcinoma in situ; HR, hazard ratio; IC, ileal conduit; IPTW, inverse probability of treatment weighting; MIS, minimally invasive surgery; NB, neobladder; pN, pathologic N stage; PSM, propensity score matching; pT, pathologic T stage; UC, ureterocutaneostomy; UD, urinary diversion.

Table 3
Potential confounding factors examined in previous researches.

Author	Patient characteristics	Pathologic features	Treatment factors
Huguet <i>et al.</i> (2008) ^[9]	—	Previous history of NMIBC* Pathologic T stage* Carcinoma in situ Prostatic urethral involvement* Prostatic stromal invasion*	Urinary diversion type
Cho <i>et al.</i> (2009) ^[12]	Age at surgery	Pathologic T stage Pathologic grade Carcinoma in situ Prostatic stromal invasion* Prostatic urethral Involvement* Multifocal disease Urethral margin* Bladder neck involvement Trigone involvement Size	—
Boorjian <i>et al.</i> (2011) ^[6]	Age at surgery Smoking	Pathologic T stage Carcinoma in situ Prostatic urethral involvement* Multifocal disease*	Urinary diversion type* Year of cystectomy
Perlis <i>et al.</i> (2013) ^[11]	Age at surgery (group) Sex	Primary T stage Pathologic T stage* Pathologic N stage Pathologic grade Carcinoma in situ Prostatic urethra involvement* Lymphovascular invasion	Urinary diversion type
Balci <i>et al.</i> (2015) ^[10]	—	Pathologic T stage* Pathologic N stage Pathologic grade Prostatic stromal invasion Multifocal disease Bladder neck involvement	Urinary diversion type
Khanna <i>et al.</i> (2021) ^[8]	Age at surgery Charlson Comorbidity Index	Pathologic T stage Pathologic N stage Carcinoma in situ* Prostatic urethral involvement* Multifocal disease* Urethral margin	Urinary diversion type* Year of surgery Neoadjuvant chemotherapy
Present study	Age at surgery (group) Smoking Body mass index ASA score	Pathologic T stage Pathologic N stage Carcinoma in situ Prostatic urethral involvement* Prostatic stromal invasion Multifocal disease	Urinary diversion type* Surgical approach (MIS vs. Open) Neoadjuvant chemotherapy Adjuvant chemotherapy

ASA, American Society of Anesthesiologists; MIS, minimally invasive surgery; NMIBC, nonmuscle-invasive bladder cancer.

*Significant variable for urethral recurrence in each study.

our study cohort did not yield statistically significant evidence of a difference in OS between patients with UR and those without disease recurrence (Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/JS9/B346>).

This study had several limitations. First, despite effectively addressing selection bias using methodologies involving propensity scores to construct a well-balanced dataset, retrospective studies have inherent limitations in controlling for unobserved confounders and establishing clear causal relationships. It is important to acknowledge that PSM and IPTW, while valuable tools, cannot completely eliminate the potential influence of unmeasured variables. Nevertheless, because randomized controlled trials are not feasible in this area of research, we believe that the combination of PSM and IPTW provides the most robust method for addressing selection bias and comparing outcomes between patients who received nonorthotopic UD and NB, given the available data and our careful consideration of known confounders. Second, to account for the significant age variations between the two groups and minimize data loss, participants were categorized into 'older adults' and 'non-older adults' using an age cutoff of 60 years, resulting in the creation of balanced matched groups. This approach ensured comparability within each age group and reduced potential data loss associated with age disparities, leading to an improved overall dataset balance. Finally, because this study was conducted at a single institution, its generalizability may be limited. The patient population, treatment, and surveillance protocols at our institution may differ from those of other institutions, potentially affecting the external validity of our findings. Further validation of these findings through prospective and multicenter studies is warranted, and additional investigations into the underlying biological mechanisms are recommended to enhance our understanding of this topic.

Conclusions

Our findings suggest significantly improved UR-free survival in patients with NB compared with those with IC/UC. Furthermore, the NB reconstruction consistently demonstrated independent protective effects against UR. These results provide compelling evidence for the protective effect of NB reconstruction in reducing UR incidence, regardless of the potential biases associated with treatment selection (Table 2).

Ethical approval

This study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Korea (IRB File No. 2023-07-106).

Consent

The requirement for written informed consent waived because of the retrospective design of this study. All study protocols were performed in accordance with the Declaration of Helsinki and all patient data complied with relevant privacy regulations and data protection.

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None.

Author contribution

J.Y. and H.H.S.: conceptualization and data curation; J.Y., C.U.L., J.H.C.: formal analysis; funding acquisition: none; J.Y., C.U.L., H.H.S.: investigation; J.Y., C.U.L., J.H.C., W.S., H.H.S.: methodology; H.H.S.: project administration; resources: none; software: none. B.C.J., S.I.S., S.S.J., H.H.S.: supervision; H.G.J., B.C.J., S.I.S., S.S.J.: validation; J.Y. and W.S.: visualization; J.Y., J.H.C., W.S., M.K., H.G.J.: writing – original draft; B.C.J., S.I.S., S.S.J., H.H.S.: writing – review and editing.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

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Data availability statement

The underlying data from the electronically database is available on demand.

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References

- [1] Witjes JA, Bruins HM, Cathomas R, *et al.* European Association of Urology Guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. *Eur Urol* 2021;79:82–104.
- [2] Herr HW. Extravesical tumor relapse in patients with superficial bladder tumors. *J Clin Oncol* 1998;16:1099–102.
- [3] Denzinger S, Mohren K, Knuechel R, *et al.* Improved clonality analysis of multifocal bladder tumors by combination of histopathologic organ mapping, loss of heterozygosity, fluorescence in situ hybridization, and p53 analyses. *Hum Pathol* 2006;37:143–51.
- [4] Freeman JA, Tarter TA, Esrig D, *et al.* Urethral recurrence in patients with orthotopic ileal neobladders. *J Urol* 1996;156:1615–9.
- [5] Kassouf W, Spiess PE, Brown GA, *et al.* Prostatic urethral biopsy has limited usefulness in counseling patients regarding final urethral margin status during orthotopic neobladder reconstruction. *J Urol* 2008;180:164–7.
- [6] Boorjian SA, Kim SP, Weight CJ, *et al.* Risk factors and outcomes of urethral recurrence following radical cystectomy. *Eur Urol* 2011;60:1266–72.
- [7] Djaladat H, Mitra AP, Miranda G, *et al.* Radical cystectomy and orthotopic urinary diversion in male patients with pT4a urothelial bladder carcinoma: oncological outcomes. *Int J Urol* 2013;20:1229–33.
- [8] Khanna A, Zganjar A, Lyon T, *et al.* A contemporary analysis of urethral recurrence following radical cystectomy. *J Urol* 2021;206:970–7.
- [9] Huguet J, Monllau V, Sabate S, *et al.* Diagnosis, risk factors, and outcome of urethral recurrences following radical cystectomy for bladder cancer in 729 male patients. *Eur Urol* 2008;53:785–92; discussion 92–3.
- [10] Balci U, Dogantekin E, Ozer K, *et al.* Patterns, risks and outcomes of urethral recurrence after radical cystectomy for urothelial cancer; over 20 year single center experience. *Int J Surg* 2015;13:148–51.
- [11] Perlis N, Turker P, Bostrom PJ, *et al.* Upper urinary tract and urethral recurrences following radical cystectomy: review of risk factors and outcomes between centres with different follow-up protocols. *World J Urol* 2013;31:161–7.
- [12] Cho KS, Seo JW, Park SJ, *et al.* The risk factor for urethral recurrence after radical cystectomy in patients with transitional cell carcinoma of the bladder. *Urol Int* 2009;82:306–11.
- [13] Fahmy O, Khairul-Asri MG, Schubert T, *et al.* Urethral recurrence after radical cystectomy for urothelial carcinoma: a systematic review and meta-analysis. *Urol Oncol* 2018;36:54–9.
- [14] Nieder AM, Sved PD, Gomez P, *et al.* Urethral recurrence after cystoprostatectomy: implications for urinary diversion and monitoring. *Urology* 2004;64:950–4.
- [15] Chan Y, Fisher P, Tilki D, *et al.* Urethral recurrence after cystectomy: current preventative measures, diagnosis and management. *BJU Int* 2016;117:563–9.
- [16] Mathew G, Agha R, Albrecht J, *et al.* STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. *Int J Surg* 2021;96:106165.
- [17] Gaya JM, Matulay J, Badalato GM, *et al.* The role of preoperative prostatic urethral biopsy in clinical decision-making at the time of radical cystectomy. *Can J Urol* 2014;21:7228–33.
- [18] Roth B, Furrer MA, Giannakis I, *et al.* Positive pre-cystectomy biopsies of the prostatic urethra or bladder neck do not necessarily preclude orthotopic bladder substitution. *J Urol* 2019;201:909–15.
- [19] EAU Guidelines. Edn. Presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6.
- [20] Chang SS, Bochner BH, Chou R, *et al.* Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. *J Urol* 2017;198:552–9.
- [21] Dellis AE, Demonakou M, Papatsoris AG, *et al.* Insight into long-term histological, proliferative and apoptotic modifications in ileal orthotopic neobladder and conduit mucosa. *Tumori* 2008;94:701–5.
- [22] Niegisch G, Hulsbergen-van de Kaa C, Ploeg M, *et al.* Do orthotopic ileal diversions induce immunological changes in retained urethral tissue? *Bladder Cancer* 2015;1:97–103.
- [23] Donat SM, Genega EM, Herr HW, *et al.* Mechanisms of prostatic stromal invasion in patients with bladder cancer: clinical significance. *J Urol* 2001;165:1117–20.
- [24] Yao Z, Jiang Y, Zhu X, *et al.* Risk factors and oncological outcomes of urethral recurrence in male patients with muscle invasive bladder cancer after radical cystectomy combined with urinary diversion: a propensity score-matched case control study. *Int J Clin Oncol* 2020;25:1377–84.
- [25] Lebre T, Herve JM, Yonneau L, *et al.* After cystectomy, is it justified to perform a bladder replacement for patients with lymph node positive bladder cancer? *Eur Urol* 2002;42:344–9; discussion 9.
- [26] Lebre T, Herve JM, Barre P, *et al.* Urethral recurrence of transitional cell carcinoma of the bladder. Predictive value of preoperative latero-montanal biopsies and urethral frozen sections during prostatocystectomy. *Eur Urol* 1998;33:170–4.
- [27] Soukup V, Babjuk M, Bellmunt J, *et al.* Follow-up after surgical treatment of bladder cancer: a critical analysis of the literature. *Eur Urol* 2012;62:290–302.