Effect of continuous saline bladder irrigation with concomitant single instillation of chemotherapy after transurethral resection on intravesical recurrence in patients with non-muscle-invasive bladder cancer

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Abstract. A single immediate instillation of chemotherapy following transurethral resection of bladder tumor (TURBT) is effective in preventing intravesical recurrence (IVR) in patients with non-muscle-invasive urothelial bladder carcinoma (NMIBC). However, continuous saline bladder irrigation (CSBI) is also performed with a single instillation of chemotherapy (SIC), but its inhibitory effect on IVR remains unclear. In the present study, the effect of CSBI with concomitant SIC following TUR on IVR was evaluated in patients with NMIBC. A retrospective review of 253 patients who underwent TURBT and were clinically and histologically diagnosed with NMIBC at National Defense Medical College Hospital was performed. Doxorubicin (DXR) was administered to all patients. Methods of DXR administration included a single instillation of DXR (60 mg in 30-40 ml saline) in 34 patients (group A), continuous irrigation of the bladder with saline including DXR (80 mg in 1 liter saline) in 40 patients (group B) and overnight CSBI after a single instillation of DXR in 179 patients (group C). The difference in IVR-free survival rates was compared after adjusting for significant differences in several covariates between the groups by nearest-neighbor propensity score matching. Prior to propensity score matching, it was identified that time to IVR was significantly longer in group A than in groups B and C; however, it was observed that several factors significantly differed among the three groups. By using nearest neighbor matching, 18 pairs were matched between groups A and B and 33 pairs between the groups A and C. No significant difference was identified in any covariates between these two matched group pairsTime to IVR was significantly longer in the matched group A than in the matched groups B and C (P=0.0255 and P=0.0023, respectively). In conclusion, SIC alone could provide a higher IVR-free survival rate than CSBI with DXR or CSBI with SIC.

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Introduction

Bladder cancer can present in different pathological stages. Approximately 80% of all bladder cancers initially present as non-muscle-invasive bladder carcinoma (NMIBC) (1). Transurethral resection of bladder tumor (TURBT) is known as the gold standard therapeutic method for NMIBC; however, the recurrence rate ranges between 40 and 80% regardless of complete resection (2). The risk of recurrence and progression of NMIBC can be predicted and calculated for each patient using the risk score suggested by the European Organization for Research and Treatment of Cancer (3).

It is thought that just within a few hours after TURBT, the free-floating tumor cells become firmly integrated to nearby structures and are covered by extracellular matrix (4). Reportedly, one of the mechanisms of early NMIBC recurrence after TURBT might be the dissemination of free-floating tumor cells during surgery, with the subsequent implantation of these cells after TURBT (5).

As NMIBC may recur and progress to muscle-invasive cancer after initial treatment (1), there is a need for efficient therapeutic strategies to decrease possible recurrence and/or progression. An immediate single instillation of chemotherapy (SIC) after TURBT is broadly recognized as an effective preventive measure for intravesical recurrence (IVR) in patients with NMIBC. This measure is especially effective among those with low- or intermediate-risk NMIBC and with low-grade Ta NMIBC according to the European Association of Urology (EAU) and American Urological Association (AUA) guidelines, respectively (4,6). Nevertheless, many urologists still hesitate to apply SIC to patients with NMIBC because the procedure is costly, may involve special postoperative care, and could result in unexpected lower urinary tract symptoms, including micturition pain, irritability reactions, and extravasation of intravesical chemotherapy agents (7,8).

Conversely, continuous saline bladder irrigation (CSBI) is another therapeutic and inhibitory option for IVR.

Onishi *et al* (9) have hypothesized that CSBI after TURBT remove floating tumor cells and prevent tumor cells from implanting on the bladder wall. They have concluded that CSBI after TURBT may be a feasible prophylactic and therapeutic option for patients with low- to intermediate-risk NMIBC (9). In a previous retrospective study, Onishi *et al* (10) have shown that CSBI after TURBT has a preventive effect on IVR of NMIBC.

Urologists have been frequently performing CSBI immediately after SIC at our institution. The objective is to prevent catheter obstruction or genitourinary infection. In the present study, we evaluated whether the combined treatment of CSBI with concomitant SIC after TURBT has an inhibitory effect on IVR in patients with NMIBC.

Patients and methods

Patients. We performed a retrospective review of the medical records of 253 patients who underwent TURBT between January 2010 and February 2018. Patients were clinically diagnosed with NMIBC, and the diagnosis was histologically confirmed as urothelial carcinoma with or without other tumor cell types at our institution. Processing of resected specimens was performed according to standard pathological procedures. The pathological staging of the primary tumor (pT) was determined according to the American Joint Committee on Cancer TNM Classification (11), whereas tumor grading was determined according to the 2004 WHO classification of urothelial tumors (12). Patients were followed up for at least 3 months postoperatively at our institution.

Our institutional ethics committee approved the study protocol (ID 2734) on June 14, 2017. An opt-out approach on the web page of the National Defense Medical College was used rather than collecting written informed consent from all participants. A total of 198 men and 55 women with a median age of 74 years (range, 33-98 years) were included in the present study. The median follow-up period after TURBT was 32.9 months (range, 3.1-98.6 months).

Doxorubicin (DXR) was administered to all patients immediately after TURBT, and all patients underwent either adjuvant intravesical chemotherapy or immunotherapy. Patients received DXR by three methods of administration: A single instillation of DXR (60 mg in 30-40 ml saline) in 34 patients (group A); CSBI with DXR 80 mg (80 mg in 1 liter saline) in 40 patients (group B); and overnight CSBI after a single instillation of DXR in 179 patients (group C). The difference between groups B and C was that patients in group B were treated with continuous irrigation of the bladder with saline including DXR (80 mg in 1 liter saline), whereas those in group C were treated with continuous bladder irrigation with saline after a single instillation of chemotherapy (SIC). Additional pathological and clinical data are shown in Table I.

Statistical analysis. Fisher's exact probability test and Kruskal-Wallis test were used to evaluate significant differences in clinicopathological factors among patients in groups A, B and C. IVR-free survival curves were constructed using the Kaplan-Meier method, and the statistical differences among the groups were evaluated using the log-rank test. Additionally, univariate and multivariate analysis was performed using Cox's proportional hazards model before propensity score matching. Nearest-neighbor propensity score matching was conducted using multiple logistic regression analysis. For this, we designated group A and B or group A and C as dependent variables, and all covariates shown in tables as explanatory variables. Further, the difference in IVR-free survival rates was also compared using the log-rank test after adjusting for significant differences in several covariates between the groups by nearest-neighbor propensity score matching. Fisher's exact probability test and Mann-Whitney U test were used to evaluate significant differences in clinicopathological factors between the matched groups A and B and matched groups A and C. Statistical analyses were performed with JMP Pro 11 (SAS Institute). A P-value <0.05 was considered statistically significant.

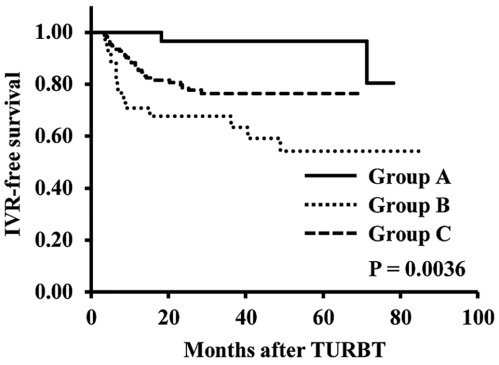

Figure 1. IVR-free survival time in groups A, B and C. There was a significant difference in time to IVR among patients treated with a single instillation of DXR (group A), continuous irrigation of the bladder with saline including DXR (group B) and a single instillation of DXR plus continuous saline bladder irrigation (group C; P=0.0036). IVR, intravesical recurrence; DXR, doxorubicin; TURBT, transurethral resection of bladder tumor.

Results

Intravesical recurrence (IVR)-free survival time among groups and independent factors for shortened time to IVR. Prior to propensity score matching, we found that time to IVR was significantly longer in the group A than in the groups B and C (P=0.0036) (Fig. 1). Additionally, a multivariate analysis using Cox's proportional hazards model showed that CSBI (groups B and C) was a significant independent factor for shorter time to IVR [group A to B: Hazard ratio (HR), 8.905; 95% confidence interval (CI), 2.450-57.106; P<0.001, and group A to C: HR, 4.193; 95% CI, 1.236-26.212; P=0.018] (Table II). Several other factors, including positive urine cytology, tumor history, pathological tumor stage, presence of CIS, and adjuvant therapeutic drugs, significantly differed among the three groups (P=0.003, P=0.003, P=0.036, P=0.011 and P=0.010, respectively) (Table I).

Nearest-neighbor propensity score matching. We calculated the predicted probability as a propensity score using multiple logistic regression analysis. By using nearest-neighbor matching, we matched 18 pairs between groups A and B and 33 pairs between groups A and C. Notably, we did not find significant differences in any covariates between the matched groups A and B and matched groups A and C (Tables III and IV). There was not any statistical

Table I. Clinicopathological characteristics of the enrolled patients.

Parameters	Immediate instillation alone, n (%) (n=34)	Saline irrigation including doxorubicin, n (%) (n=40)	Immediate instillation plus saline irrigation, n (%) (n=179)	P-value
Age, years (range)	74.5 (46-92)	71.5 (42-89)	74 (33-98)	0.343
Sex				0.146
Men	22 (64.7)	32 (80.0)	144 (80.4)	
Women	12 (35.3)	8 (20.0)	35 (19.6)	
Urine cytology				0.003
≥3b	11 (33.3)	14 (35.0)	103 (58.2)	
≤3a	22 (66.7)	26 (65.0)	74 (41.8)	
Smoking history				0.146
Positive	18 (52.9)	30 (79.0)	115 (66.9)	
Negative	16 (47.1)	8 (21.0)	57 (33.1)	
History of UTUC				0.339
Positive	3 (8.8)	6 (15.0)	13 (7.3)	
Negative	31 (91.2)	34 (85.0)	166 (92.7)	
First or recurrent tumor				0.003
Recurrent	12 (35.3)	17 (42.5)	33 (18.4)	
First	22 (64.7)	23 (57.5)	146 (81.6)	
Solitary or multiple tumors				0.784
Multiple	22 (64.7)	27 (67.5)	126 (70.4)	
Solitary	12 (35.3)	13 (32.5)	53 (29.6)	
Histology				0.317
UC and other subtypes	1 (2.9)	4 (10.0)	18 (10.1)	
UC alone	33 (97.1)	36 (90.0)	161 (89.9)	
pT status				0.036
pTis	6 (17.7)	0 (0.0)	16 (8.9)	
pT1	11 (32.3)	18 (45.0)	67 (37.4)	
pTa	17 (50.0)	22 (55.0)	96 (53.7)	
Tumor grade				0.205
High or G3	23 (67.7)	23 (57.5)	129 (72.1)	
PUNLMP/low	11 (32.3)	17 (42.5)	50 (27.9)	
CIS				0.011
Positive	10 (29.4)	5 (12.5)	63 (35.2)	
Negative	24 (70.6)	35 (87.5)	116 (64.8)	
Adjuvant therapy				0.010
BCG	23 (67.7)	15 (37.5)	111 (62.0)	
Chemotherapeutic drugs	11 (32.3)	25 (62.5)	68 (38.0)	

UT, upper urinary tract; UC, urothelialcarcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential; CIS, carcinoma *in situ*; BCG, bacillus Calmette-Guérin.

difference in the factors on the violin plots between matched groups A and B (Fig. 2A) or between matched groups A and C (Fig. 2B). We did observe that time to IVR was significantly longer in matched group A than in matched groups B and C (P=0.0255 and P=0.0023, respectively) (Fig. 3A and B). In addition, the number of patients in each group was decreased to diminish a significant difference in each factor between the groups using nearest neighbor matching. That is why the patients were censored at different times (Fig. 3A and B). The hazard ratio was 7.72 in the pairs matched between the groups A and B and 12.49 in the pairs matched between the groups A and C using Cox's proportional hazards model (data not shown).

Discussion

In the multivariate analysis using Cox's proportional hazards model without propensity score matching, patients in the present

Table II. Univariate and multivariate analyses of independent factors for IVR-free survival.

	Univariate		Multivariate		
Pathological measurements	Hazard ratio	P-value	Hazard ratio	95% CI	P-value
Age (<74 or ≥74 years)	1.030	0.063	1.030	0.996-1.065	0.082
Sex (male or female)	1.020	0.953			
Smoking history (positive or negative)	0.995	0.987			
History of UTUC (positive or negative)	0.642	0.457			
Urine cytology (positive or negative)	1.957	0.021	2.106	1.150-3.963	0.016
Tumor history (recurrent or primary)	1.792	0.061	1.855	0.947-3.522	0.071
Tumor multiplicity (multiple or single)	1.393	0.294			
Histology (UC with others or UC alone)	0.958	0.934			
Pathological T stage (T1 or Ta or Tis)	1.411	0.279			
Tumor grade (G3/high or PUNLMP/low)	1.752	0.096			
Carcinoma *in situ* (positive or negative)	0.923	0.799			
Adjuvant therapy (BCG or chemotherapeutic drug)	1.112	0.717			
Immediate instillation method (A or B or C)	8.424	0.002	8.905	2.450-57.106	<0.001

IVR, intravesical recurrence; UC, urothelial carcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential; CIS, carcinoma *in situ*; BCG, bacillus Calmette-Guérin; A, a single instillation of DXR; B, continuous irrigation of the bladder with saline including DXR; C, a single instillation of DXR plus continuous saline bladder irrigation; DXR, doxorubicin.

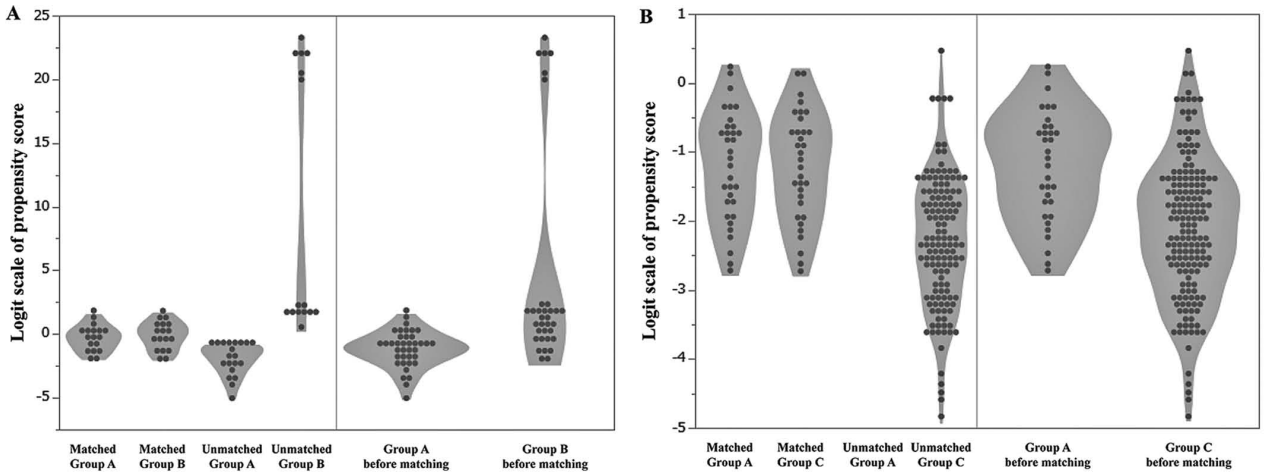

Figure 2. Violin plots of matched groups. Violin plots of the matched and unmatched groups as well as the groups before matching showed the distribution of dots based on the logit scale of the propensity score, which can be compared between matched groups. The violin plot did not reveal any difference in the factors between (A) matched groups A and B or (B) matched groups A and C.

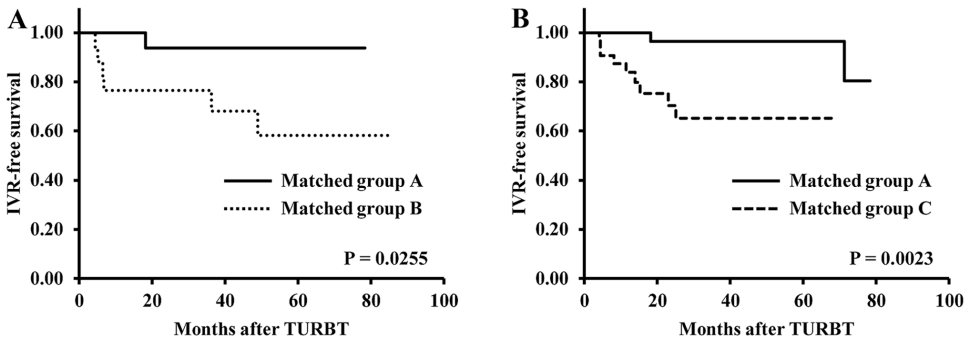

Figure 3. IVR-free survival time in matched groups. (A) There was a significant difference in time to IVR between patients treated with a single instillation of DXR (matched group A) and continuous irrigation of the bladder with saline including DXR (matched group B; P=0.0255). (B) Additionally, a significant difference was observed between patients treated with a single instillation of DXR (matched group A) and a single instillation of DXR plus continuous saline bladder irrigation (matched group C; P=0.0023). IVR, intravesical recurrence; DXR, doxorubicin; TURBT, transurethral resection of bladder tumor.

Table III. Characteristics of patients matched on propensity score.

Parameters	Immediate instillation alone, n (%) (n=18)	Saline irrigation including DXR, n (%) (n=18)	P-value
Age, years (range)	71 (46-92)	75 (42-82)	0.787
Sex			0.479
Male	11 (61.1)	13 (72.2)	
Female	7 (38.9)	5 (27.8)	
Urine cytology			>0.999
≥3b	13 (72.2)	13 (72.2)	
≤3a	5 (27.8)	5 (27.8)	
Smoking history			0.479
Positive	11 (61.1)	13 (72.2)	
Negative	7 (38.9)	5 (27.8)	
History of UTUC			0.543
Positive	2 (11.1)	1 (5.6)	
Negative	16 (88.9)	17 (94.4)	
First or recurrent tumor			0.717
Recurrent	5 (27.8)	6 (33.3)	
First	13 (72.2)	12 (66.7)	
Solitary or multiple tumors			0.729
Multiple	12 (66.7)	11 (61.1)	
Solitary	6 (33.3)	7 (38.9)	
Histology			0.543
UC and other subtypes	1 (5.6)	2 (11.1)	
UC alone	17 (94.4)	16 (88.9)	
pT status			>0.999
pTis	0 (0.0)	0 (0.0)	
pT1	8 (44.4)	8 (44.4)	
pTa	10 (55.6)	10 (55.6)	
Tumor grade			0.735
High or G3	11 (61.1)	10 (55.6)	
PUNLMP/low	7 (38.9)	8 (44.4)	
CIS			>0.999
Positive	2 (11.1)	2 (11.1)	
Negative	16 (88.9)	16 (88.9)	
Adjuvant therapy			0.738
BCG	10 (55.6)	9 (50.0)	
Chemotherapeutic drugs	8 (44.4)	9 (50.0)	

DXR, doxorubicin; UT, upper urinary tract; UC, urothelialcarcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential; CIS, carcinoma *in situ*; BCG, bacillus Calmette-Guérin.

study treated with SIC alone (group A) showed a significantly higher IVR-free survival rate than those treated with CSBI including DXR (group B), and SIC plus CSBI (group C). Even after matching using the nearest-neighbor propensity score, patients of matched group A had a significantly higher IVR-free survival rate than those of matched groups B and C. Actually, no difference was observed in the time to intravesical recurrence between groups B and group C before and after propensity score matching. However, significant differences in some factors were observed between these two groups, as shown in Table I; thus, we speculated that we would need to adjust the patients' background using nearest neighbor matching.

As high IVR rates are not uncommon after TURBT in patients with NMIBC, preventive treatments for IVR are required. Gudjónsson *et al* (13) showed that SIC with epirubicin after TURBT had an inhibitory effect on disease recurrence in patients with NMIBC at low to intermediate risk. Moreover, Sylvester *et al* (14) performed the first meta-analysis of SIC and

Table IV. Characteristics of patients matched on propensity score.

Parameters	Immediate instillation alone, n (%) (n=33)	Immediate instillation plus saline irrigation, n (%) (n=33)	P-value
Age (range)	75 (46-92)	74 (50-85)	0.724
Sex			>0.999
Male	21 (63.6)	21 (63.6)	
Female	12 (36.4)	12 (36.4)	
Urine cytology			0.609
≥3b	11 (33.3)	13 (39.4)	
≤3a	22 (66.7)	20 (60.6)	
Smoking history			>0.999
Positive	17 (51.5)	17 (51.5)	
Negative	16 (48.5)	16 (48.5)	
History of UTUC			0.641
Positive	3 (9.1)	2 (6.1)	
Negative	30 (90.9)	31 (93.9)	
First or recurrent tumor			0.609
Recurrent	11 (33.3)	13 (39.4)	
First	22 (66.7)	20 (60.6)	
Solitary or multiple tumors			0.796
Multiple	21 (63.6)	22 (66.7)	
Solitary	12 (36.4)	11 (33.3)	
Histology			0.236
UC and other subtypes	1 (3.0)	0 (0.0)	
UC alone	32 (97.0)	33 (100.0)	
pT status			0.784
pTis	6 (18.2)	8 (24.2)	
pT1	11 (33.3)	9 (27.3)	
pTa	16 (48.5)	16 (48.5)	
Tumor grade			0.792
High or G3	22 (66.7)	23 (69.7)	
PUNLMP/low	11 (33.3)	10 (30.3)	
CIS			0.601
Positive	10 (30.3)	12 (36.4)	
Negative	23 (69.7)	21 (63.6)	
Adjuvant therapy			0.609
BCG	22 (66.7)	20 (60.6)	
Chemotherapeutic drugs	11 (33.3)	13 (39.4)	

UT, upper urinary tract; UC, urothelialcarcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential; CIS, carcinoma *in situ*; BCG, bacillus Calmette-Guérin.

noted that SIC clearly lead to a reduction in IVR compared to TURBT alone in patients with NMIBC. The same group recently reported that a SIC after TURBT reduced the risk of disease recurrence, with a decrease in the 5-year recurrence rate from 58.8 to 44.8% (15). Therefore, EAU as well as AUA guidelines have currently recommended performing SIC immediately after TURBT in patients with NMIBC (4,6). Despite these recommendations and the benefits of SIC for patients with NMIBC shown in previous randomized controlled trials and a meta-analysis of SIC (8,16), the use of SIC after TURBT remains under discussion. In fact, a study in European countries found that SIC after TURBT was performed in only 33-43% of patients with NMIBC in that setting (17).

In contrast, earlier reports suggested that CSBI had a greater preventive effect on IVR compared to SIC (9,10,18,19). One report showed that there were no significant differences in the median time to first recurrence between patients treated with CSBI and those who underwent immediate SIC with mitomycin C (9). Another study revealed that CBSI with sterile water after TURBT might have the same preventive effect on

IVR as an immediate single dose of intravesical mitomycin C in patients with NMIBC (18).

Our findings have some clinical implications. First, although several studies reported no significant difference in time to IVR between patients treated with CSBI alone and those treated with SIC (9,10,18), our results suggest that CSBI can weaken the inhibitory effect of SIC on IVR if it is performed after SIC. Second, irrigation with saline and DXR, which included a low concentration of DXR, did not exert an anticancer effect, meaning that CSBI alone could not have a preventive effect on IVR. We speculated that intravesical irrigation should have the possibility of washing tumor cells out of the bladder; however, it is possible that the urine flow following SIC could lead to higher IVR-free survival rates.

This study has some potential limitations. First, our sample size was relatively small, particularly in groups A and B. A larger number of patients treated with SIC alone, CSBI after SIC, and CSBI with DXR would have yielded more robust results than those obtained, even after applying nearest-neighbor propensity score matching. Second, although CSBI alone has been reported to show a preventive effect on IVR (9,10), we could not clarify the reason why CSBI after SIC did not show an inhibitory effect on IVR in this study. Third, the effect of the second TUR was not evaluated in the present study because the number of patients who underwent a second TUR was relatively small.

We found a higher IVR rate in patients with NMIBC treated with CSBI irrespective of whether they received concomitant SIC or CSBI with DXR, compared with patients treated with a SIC alone. To the best of our knowledge, ours is the first paper concluding that SIC alone can provide a higher IVR-free survival rate than CSBI with DXR or CSBI with SIC. Further prospective studies having a larger number of patients with NIMBC should be conducted to confirm the abovementioned finding and thus to validate SIC alone as an IVR prevention method.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KK, ST, AS, JA, AH and KI were involved in the conception and design of the study. KK collected and analyzed the data, and drafted the manuscript. KK and KI reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of National Defense Medical College (approval no. 2734). All procedures were conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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