

# Dysuria therapeutic agents as an independent prognostic factor for the primary recurrence of non-muscle invasive bladder cancer: a propensity score matching study

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## Abstract

**Objective:** To investigate if the use of therapeutic agents for dysuria is a risk factor for the primary recurrence of non-muscle invasive bladder cancer (NMIBC).

**Methods:** First, patients with NMIBC were divided into two groups: the non-recurrence group and the recurrence group. Patient characteristics were compared between both groups. The risk factors of recurrence that were statistically different between the two groups were identified by multivariate analysis. Second, we divided the patients into risk and non-risk groups, and differences in the recurrence-free survival (RFS) between the two groups were analyzed before and after propensity score matching (PSM).

**Results:** A total of 162 patients were included, with 84 patients in the non-recurrence group and 78 patients in the recurrence group. In the multivariate analysis, the intake of dysuria agents and bacillus Calmette–Guérin (BCG) therapy were independent factors. The RFS results in terms of the intake of dysuria agents were statistically significant before and after PSM analysis, but no factors were significantly different between the BCG and non-BCG groups after PSM.

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**Conclusions:** Therapeutic agents for dysuria might be at an independent risk factor for NMIBC recurrence. This trial is registered with the UMIN Clinical Trials Registry under the number UMIN000036097 ([https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr\\_view.cgi?recptno=R000041122](https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000041122)).

### Keywords

Bladder cancer, non-muscle invasive, dysuria, recurrence, propensity score matching study, residual urine

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## Introduction

Non-muscle invasive bladder cancer (NMIBC) accounts for approximately 70% of bladder cancer patients, with transurethral resection of the bladder tumor (TURBT) as the primary treatment choice.<sup>1</sup> Intravesical bacillus Calmette–Guérin (BCG) therapy is currently the standard adjuvant therapy for NMIBC after TURBT as it significantly reduces the risk of disease recurrence or progression.<sup>1</sup> Despite receiving BCG therapy, 30% to 50% of patients fail to respond, and 15% of patients display muscle-invasive disease progression.<sup>2</sup>

Smoking,<sup>3–5</sup> exposure to aromatic amines<sup>6,7</sup> and ingestion of some lactic acid bacteria<sup>8,9</sup> are generally considered risk factors. The European Organization for Research and Treatment of Cancer (EORTC) and the Spanish Urological Club for Oncological Treatment (CUETO) have determined risk categories for the recurrence and progression of bladder cancer that are based on the patient's background, and the outcomes of the initial treatment are widely used.<sup>10</sup> This study investigated risk factors for the primary recurrence of NMIBC in our dataset to identify and validate recurrence factors.

## Materials and methods

### Patients

We retrospectively studied patients who underwent TURBT or intravesical BCG therapy for NMIBC at our hospital between July 2002 and September 2017. All patients provided written consent for treatment. Twenty-four patients were excluded from the study because they had been followed up for less than 6 months. Patients included in the final analyses were divided into two groups: the non-recurrence group and the recurrence group. The Ethics Committee of Iwate Medical University (Iwate, Japan) approved this clinical trial (MH2019-606) prior to patient recruitment on 25 February 2019, and the details of patients were de-identified. Moreover, the design of this retrospective study followed all relevant principles of the Declaration of Helsinki. This trial is registered with the UMIN Clinical Trials Registry under the number UMIN000036097. The reporting of this study conforms to the STROBE statement.<sup>11</sup>

### Inclusion and exclusion criteria

The inclusion criteria were patients with NMIBC ( $\leq$ pT1) with a confirmed diagnosis of urothelial carcinoma. Patients with a

negative cytology test and no residual tumors were included at the start of follow-up. The exclusion criterion was a history of primary upper urinary tract cancer (UUTC). BCG therapy during this observing period consisted of 40 or 80 mg Immunobladder (Tokyo strain BCG, Japan BCG Laboratory, Tokyo, Japan) provided as infusion therapy (up to 8 times once a week), and the dose was decided by the clinician. In addition to background characteristics, the EORTC and CUETO recurrence scores and the factors that the scores are based on were calculated for each patient, and the incidence of a second TURBT and BCG therapy, current or past medication history of therapeutic agents for dysuria and recurrence status during the follow-up period were recorded. Additionally, we conducted uroflowmetry and residual urine analysis on a subset of the patient series.

The agents for dysuria included alpha-1 blockers, tadalafil, cholinergic drugs, dutasteride, herbs and anti-androgens used to treat lower urinary tract symptoms (LUTS) during the follow-up period. Anticholinergic and beta-3 stimulants were excluded as agents for dysuria in this study. In addition, patients who were treated with agents for dysuria and had at least one diagnosis of benign prostatic hyperplasia, neurogenic bladder or prostate cancer were defined as the intake group. Moreover, cases treated with both agents for dysuria and an anticholinergic and/or beta-3 stimulant were included in the intake group. The non-intake group was defined as the group that did not receive these treatments.

### **Treatment**

TURBT was performed for obvious bladder tumors, and only carcinoma in situ cases without a visible tumor received intravesical BCG therapy. Moreover, cases

categorized as higher than intermediate risk based on the EORTC recurrence score potentially received BCG therapy. Our institute does not select maintenance BCG therapy; therefore, there were no maintenance BCG patients. We also performed a second TURBT procedure in pT1 cases or cases in which the muscle layer of the bladder wall was not captured during the initial TURBT.

### **Follow-up**

A follow-up schedule was established that included cystoscopy and urinary cytology evaluation every 3 months for the first 2 years and then at 6-month intervals for the next 3 years until recurrence. In addition, abdominal and pelvic computed tomography examinations were performed when UUTC recurrence was suspected. Recurrence was defined as the identification of urothelial carcinoma at the follow-up cystoscopy examination and biopsy, except for residual cancer identified during the second TURBT. Therefore, the follow-up period was from the first TURBT to the latest visit date.

### **Statistical analysis**

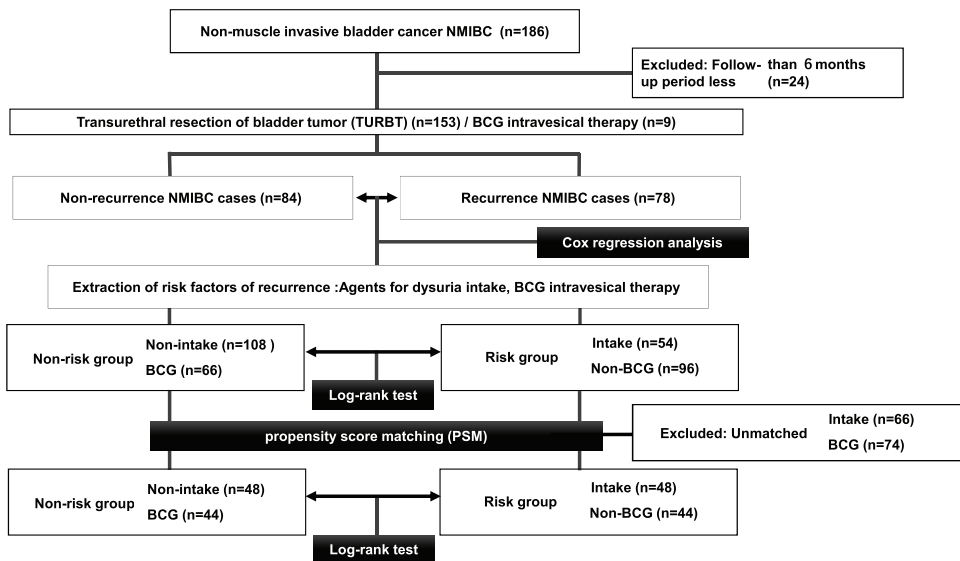
The data were analyzed using JMP<sup>®</sup> 14 statistical software (SAS Institute Inc., Cary, NC, USA). Differences between the non-recurrence and recurrence groups in terms of continuous variables, such as follow-up period and age, were analyzed using t-tests. The Cox regression test was used for categorical variables. The recurrence-free survival (RFS) was calculated using Kaplan–Meier curves, and the significance of differences between survival curves was determined using the log-rank test. Moreover, the hazard ratio (HR) was calculated using Cox regression analysis.  $p < 0.05$  was considered to indicate a statistically significant difference.

First, we performed a univariate Cox regression analysis to identify risk factors in the non-recurrence and recurrence groups. Next, a multivariate Cox regression analysis of the factors with statistically significant differences was performed. Factors with significant differences were identified. Differences in the RFS between the risk and non-risk groups were investigated by Kaplan–Meier curves before and after propensity score matching (PSM) analysis. The statistically significant factors were investigated by the PSM method. We used the PSM method to adjust the baseline differences between the risk or non-risk groups and obtain more accurate conclusions, as previously reported.<sup>12,13</sup> Moreover, we used an add-in software of JMP® in accordance with the supplier’s protocol (<http://www.jmp.com/content/dam/jmp/documents/jp/support/propensityaddin.zip>). A multivariate logistic regression analysis was used to determine the propensity scores for unbalanced variables between the risk or non-risk

groups.<sup>12,13</sup> The risk and non-risk groups were matched 1:1 using a caliper width of 0.2 of the standard deviation for the propensity score through nearest neighbor matching (greedy-matching algorithm).<sup>12</sup> We achieved a balance between the risk and non-risk groups after PSM analysis for each risk factor.

## Results

Of 186 patients retrospectively studied, 162 patients were evaluated in the final analysis, including 84 patients in the non-recurrence group and 78 patients in the recurrence group. The flowchart of patient selection based on the inclusion and exclusion criteria was shown in Figure 1. All characteristics of patients in the non-recurrence and recurrence groups were listed in Table 1. The follow-up period was 477.7 (75.6–1079.6) months in the non-recurrence group and 187.4 (34.0–919.6) months in the recurrence group ( $p < 0.001$ ). In



**Figure 1.** Flowchart of patient selection based on the inclusion and exclusion criteria in this study NMIBC, non-muscle invasive bladder cancer; TURBT, transurethral resection of bladder tumors; BCG, bacillus Calmette–Guerin; PSM, propensity score matching.

**Table 1.** Patient characteristics of the non-recurrence group and recurrence group

Variable	Univariate analysis			Multivariate analysis	
	Non-recurrence group	Recurrence group	Risk ratio (95%CI)	p-value	Risk ratio (95% CI) p-value
Number of patients (%)	84 (100)	78 (100)			
Follow-up period, months	477.7 (75.6–1079.6)	187.4 (34.0–919.6)		<0.001*	
Age >70 (years)	37	41	1.2593 (0.8060–1.9728)	0.310 <sup>†</sup>	
Age, continuous (years)	67.4±11.25	70.1±11.40	3.5683 (1.2028–11.1137)	0.021*	2.0259 (0.6603–6.4826)
Number of women (%)	15 (17.9)	18 (23.1)	1.2463 (0.7146–2.0682)	0.423 <sup>†</sup>	
Agents for dysuria (%)	18 (21.4)	36 (46.2)	2.0037 (1.2764–3.1298)	0.003 <sup>†</sup>	1.8026 (1.1319–2.8576)
Past history of DM	13 (15.5)	18 (23.1)	1.5988 (0.9169–2.6520)	0.095 <sup>†</sup>	
T stage (pathology)					
Ta	43 (51.9)	37 (47.4)	Ref.		
T1	30 (35.7)	37 (47.4)	1.3222 (0.8346–2.0940)	0.233 <sup>†</sup>	
Tis	11 (13.1)	4 (5.2)	0.4754 (0.1422–1.1873)	0.119 <sup>†</sup>	
Presence of muscle layer, Yes (%)	70 (83.3)	62 (79.5)	0.9005 (0.5330–1.6150)	0.712 <sup>†</sup>	
Number of tumors					
Single	53 (63.1)	33 (42.3)	1.5619 (0.9999–2.4654)	0.050 <sup>†</sup>	1.5389 (0.9837–2.4323)
Multiple	31(36.9)	45 (57.7)			
Tumor size					
>3 cm	70 (83.3)	68 (87.2)	1.0017 (0.7859–1.2309)	0.988 <sup>†</sup>	
≤3 cm	14 (16.7)	10 (12.8)			
EORTC score					
0–4	56 (63.0)	42 (53.9)	1.4656 (0.9344–2.2869)	0.095 <sup>†</sup>	
5–11	28 (33.3)	36 (46.2)			
CUETO score					
0–4	45 (53.6)	34 (43.6)	1.292 (0.8276–2.0344)	0.260 <sup>†</sup>	
5–16	39 (46.4)	44 (56.4)			
BCG, Yes (%)	42 (50.0)	24 (30.8)	0.5468 (0.3307–0.8777)	0.012 <sup>†</sup>	0.5637 (0.3398–0.9086)
BCG (CIS) only	6 (66.7)	3 (33.3)	0.5087 (0.1245–1.3660)	0.203 <sup>†</sup>	
Second TUR, Yes (%)	46 (54.8)	37 (47.4)	0.7323 (0.4673–1.1436)	0.170 <sup>†</sup>	

DM, diabetes mellitus; EORTC, the European Organization for Research and Treatment of Cancer; CUETO, the Spanish Urological Club for Oncological Treatment; BCG, bacillus Calmette–Guerin; CIS, carcinoma in situ; TUR, transurethral resection; CI, confidence interval.

Follow-up period was expressed as the mean and (range), continuous variables with a normal distribution were reported as the mean SD, and categorical variables were reported as a number (percentage).

\*Independent-samples t-test or Student's t-test was used to compare the mean of two continuous normally distributed variables.

<sup>†</sup>Cox regression test was used for categorical variables.

addition, between the non-recurrence and recurrence groups, the number of women, past history of diabetes mellitus (DM) and presence of muscle layers in the specimen were not statistically different. Among the two groups included in the recurrent cases, the candidate recurrence factors identified in the univariate analyses were age continuous ( $p=0.021$ ), agents for dysuria ( $p=0.003$ ), number of tumors ( $p=0.050$ ) and BCG intravesical therapy ( $p=0.012$ ). Furthermore, the multivariate analysis of these four factors revealed that agents for dysuria and BCG therapy were statistically significant ( $p=0.013$  and  $p=0.018$ , respectively) (Table 1). In terms of agents for dysuria, the differences in the median RFS during the follow-up period between the non-intake and intake groups were statistically significant. Specifically, the RFS was not reached in the non-intake group and 20.2 months [95% confidence interval (CI) 10.2–36.9 months] in the intake group [HR 2.00; 95% CI 1.28–3.13] ( $p=0.002$ ) (Figure 2). Regarding the BCG status, the median RFS in the BCG group and the non-BCG group was 76.6 months (95% CI 34.0–not reached) and 31.7 months (95% CI 16.7–47.8 months), respectively. The median RFS in the BCG group was significantly longer than that in the non-BCG group [HR 0.55; 95% CI 0.33–0.88] ( $p=0.013$ ) (Figure 3).

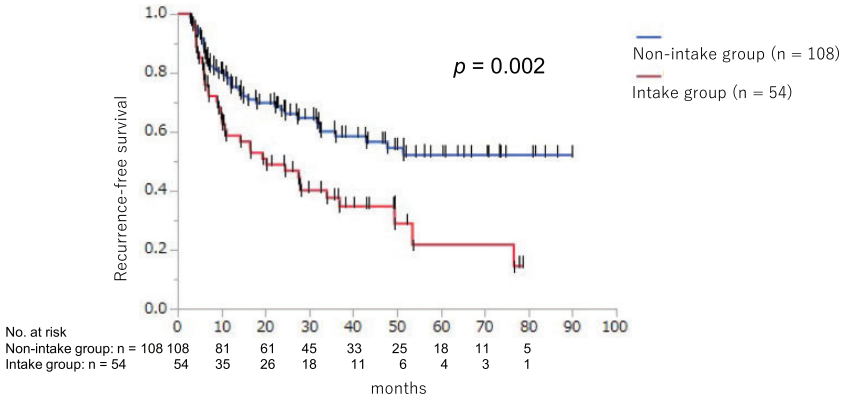
Regarding agents for dysuria, prior to the PSM analyses, the differences in age continuous ( $p=0.015$ ), number of women ( $p=0.002$ ), history of DM ( $p=0.018$ ) and presence of muscle layer ( $p=0.036$ ) between the non-intake and intake groups were statistically significant. In contrast, differences in the follow-up period, pT stages, EORTC score, CUETO score, primary intravesical BCG therapy and second TURBT between the two groups were not statistically significant (Table 2). When we achieved a balance in baseline variables between the two groups using the PSM

method, both groups consisted of 48 cases. After the PSM analyses, no variables were significantly different (Table 2).

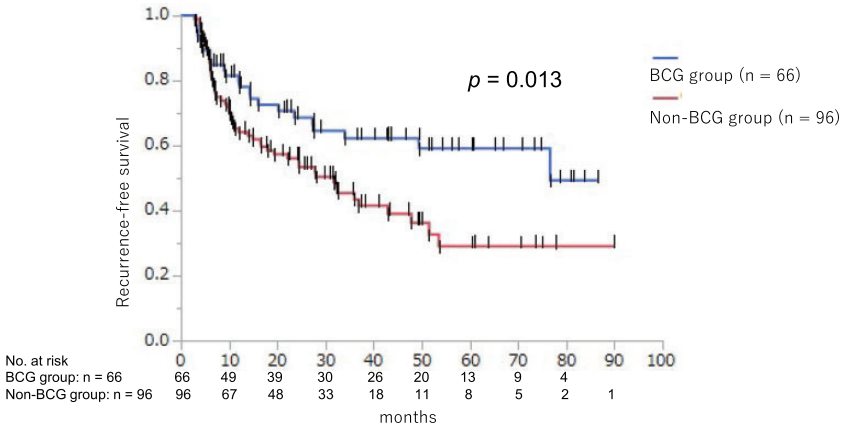
Regarding BCG therapy, the significantly different factors between the non-BCG group and BCG group prior to PSM analyses were the follow-up period ( $p=0.024$ ), age  $>70$  ( $p=0.006$ ), age continuous ( $p=0.007$ ), number of women ( $p=0.027$ ), pT stage ( $p<0.001$ ), presence of muscle layer ( $p=0.002$ ) and second TURBT ( $p=0.009$ ) (Table 3). Similar to the agents for dysuria, no factors were significantly different between the two groups after adjustments using the PSM method (Table 3).

After the PSM analyses, the median RFS was not reached in the non-intake group and 20.2 months (95% CI 10.2–34.0 months) in the intake group [HR 2.72; 95% CI 1.47–5.29] ( $p=0.001$ ) (Figure 4). In addition, the median RFS was not reached in the BCG group and 36.0 months (95% CI 19.3–not reached) in the non-BCG group [HR 0.74; 95% CI 0.38–1.41] ( $p=0.363$ ) (Figure 5).

Among the therapeutic agents in the intake group, consisting of 54 cases, alpha-1 blockers were the most frequently used, followed by herbs. No cases used tadalafil during the follow-up period. Only one case used an alpha-1 blocker, cholinergic drugs and dutasteride. There were five prostate cancer comorbidity cases. Among them, three cases were taking anti-androgens, and the other two were taking alpha-1 blockers. Therefore, all prostate cancer comorbidity cases were allocated to the intake group. Regarding the recurrence rate by the types of medication, the average recurrence rate was 66.7% (36/54), and all patients taking anti-androgens recurred (3/3) (Table 4). During this follow-up period, 10 deaths were confirmed from the medical records. Two of these patients died due to disease progression of NMIBC. No cases



**Figure 2.** Recurrence-free survival of the non-intake (n=108) and intake (n=54) groups before PSM analysis  
PSM, propensity score matching



**Figure 3.** Recurrence-free survival of the BCG (n=66) and non-BCG (n=96) groups before PSM analysis  
BCG, bacillus Calmette–Guerin; PSM, propensity score matching.

died immediately after the start of therapeutic agents for dysuria.

Moreover, the RFS was investigated in 74/162 cases who were divided into four groups based on the intake status and residual urine (cut-off volume: 50 mL). The highest recurrence rates were observed in the intake and residual urine  $\geq 50$  mL group, and the lowest recurrence rates were found in the non-intake and residual urine  $< 50$  mL group ( $p = 0.017$ ). However, when the other two groups (the non-intake

and residual urine  $\geq 50$  mL group and the intake and residual urine  $< 50$  mL group) were included, there was no statistically significant difference (Figure 6).

### Discussion

This trial was conducted to identify the recurrence risk factors from our retrospective medical records and evaluate the robustness of each factor. In the multivariate analyses, the intake of agents for

**Table 2.** Patient characteristics before and after PSM analysis in the intake and non-intake groups

Variable	Before PSM (n=162)		After PSM (n=96)		p-value
	Non-intake group	Intake group	Non-intake group	Intake group	
Number of patients (%)	108 (100)	54 (100)	48 (100)	48 (100)	
Follow-up period, months	363.8 (34.0–1079.6)	286.1 (42.0–944.4)	370.0 (34.0–1038.4)	42.6 (36.8–944.4)	0.081*
Age >70 (years)	51 (47.2)	29 (53.7)	26 (54.2)	24 (50.0)	0.683 <sup>γ</sup>
Age, continuous (years)	67.2±11.7	71.8±10.2	69.4±10.1	70.4±9.6	0.642*
Number of women (%)	29 (26.9)	4 (5.6)	4 (8.3)	4 (8.3)	1.000 <sup>γ</sup>
Past history of DM	26 (24.1)	5 (9.3)	5 (10.4)	5 (10.4)	1.000 <sup>γ</sup>
pT stage					0.605 <sup>γ</sup>
Ta	52 (47.7)	28 (52.8)	24 (50.0)	27 (56.3)	
T1	47 (43.5)	20 (37.0)	17 (35.4)	17 (35.4)	
Tis	9 (8.2)	6 (11.3)	7 (14.6)	4 (8.3)	
Presence of muscle layer, Yes (%)	93 (86.1)	39 (72.2)	38 (79.2)	39 (81.3)	0.798 <sup>γ</sup>
Number of tumors					0.064 <sup>γ</sup>
Single	61 (56.5)	25 (43.5)	31 (64.6)	22 (45.8)	
Multiple	47 (43.5)	29 (53.7)	17 (35.4)	26 (54.2)	
Tumor size					0.058 <sup>γ</sup>
>3 cm	19 (17.6)	5 (9.3)	36 (75.0)	43 (89.6)	
≤3 cm	89 (82.4)	49 (90.7)	12 (25.0)	5 (10.4)	
EORTC score					0.288 <sup>γ</sup>
0–4	67 (62.0)	31 (57.4)	33 (68.8)	28 (58.3)	
5–11	41 (38.0)	23 (42.6)	15 (31.2)	20 (41.7)	
CUETO score					0.414 <sup>γ</sup>
0–4	50 (46.3)	29 (53.7)	23 (47.9)	27 (56.3)	
5–16	58 (53.7)	25 (46.3)	25 (52.1)	21 (43.7)	
BCG, Yes (%)	44 (40.3)	22 (41.5)	23 (47.9)	18 (37.5)	0.409 <sup>γ</sup>
Second TUR, Yes (%)	61 (56.5)	22 (40.7)	26 (54.2)	21 (43.8)	0.414 <sup>γ</sup>

DM, diabetes mellitus; EORTC, the European Organization for Research and Treatment of Cancer; CUETO, the Spanish Urological Club for Oncological Treatment; BCG, bacillus Calmette–Guerin; TUR, transurethral resection; PSM, propensity score matching.

Follow-up period was expressed as the mean and (range), continuous variables with a normal distribution were reported as the mean SD, and categorical variables were reported as a number (percentage).

\*Independent-samples t-test or Student's t-test was used to compare the mean of two continuous normally distributed variables.

<sup>γ</sup>Chi-square test was used for categorical variables.



**Table 3.** Patient characteristics before and after PSM analysis in BCG and non-BCG groups.

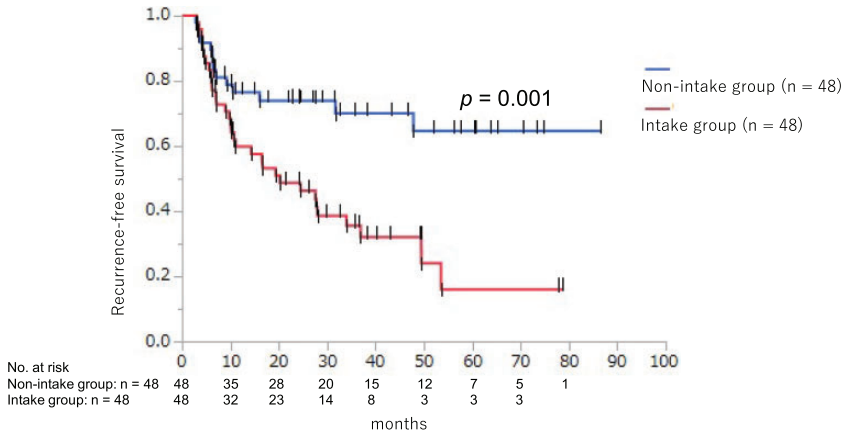
Variable	Before PSM (n=162)		After PSM (n=88)		p-value
	BCG group	Non-BCG group	BCG group	Non-BCG group	
Number of patients (%)	66 (100)	96 (100)	44 (100)	44 (100)	
Follow-up period, months	396.4 (36.8–1038.4)	297.8 (34.0–1079.6)	364.5 (36.8–972.0)	363.0 (50.4–1079.6)	0.981*
Age >70 (years)	24 (36.4)	56 (58.3)	14 (31.8)	18 (40.9)	0.375 <sup>γ</sup>
Age, continuous (years)	65.8±10.6	70.7±11.53	65.7±9.6	66.3±12.5	0.776*
Number of women (%)	8 (12.1)	25 (26.0)	8 (18.2)	8 (18.2)	1.000 <sup>γ</sup>
Agents for dysuria (%)	22 (33.3)	32 (33.3)	15 (33.3)	15 (33.3)	1.000 <sup>γ</sup>
Past history of DM	13 (19.7)	18 (18.8)	8 (18.2)	9 (20.5)	0.787 <sup>γ</sup>
pT stage					0.392 <sup>γ</sup>
Ta	18 (27.3)	62 (64.6)	18 (40.9)	22 (50.0)	
T1	33 (50.0)	34 (35.4)	26 (59.1)	22 (50.0)	
Tis	15 (22.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Presence of muscle layer, Yes (%)	46 (69.7)	86 (89.6)	36 (81.8)	38 (86.4)	0.559 <sup>γ</sup>
Number of tumors					0.830 <sup>γ</sup>
Single	33 (50.0)	53 (55.2)	20 (45.4)	19 (43.2)	
Multiple	33 (50.0)	43 (44.8)	24 (54.6)	25 (56.8)	
Tumor size					0.796 <sup>γ</sup>
>3 cm	11 (16.7)	13 (13.5)	9 (20.4)	10 (22.7)	
≤3 cm	55 (83.3)	83 (86.5)	35 (79.6)	34 (77.3)	
EORTC score					0.653 <sup>γ</sup>
0–4	34 (51.5)	64 (66.7)	30 (68.2)	28 (63.6)	
5–11	32 (48.5)	32 (33.3)	14 (31.8)	16 (36.4)	
CUETO score					0.831 <sup>γ</sup>
0–4	28 (42.4)	51 (53.1)	24 (54.6)	23 (52.3)	
5–16	38 (57.6)	45 (46.9)	20 (45.4)	21 (47.7)	
Second TUR, Yes (%)	42 (63.6)	41 (42.7)	33 (75.0)	32 (72.7)	0.808 <sup>γ</sup>

DM, diabetes mellitus; EORTC, the European Organization for Research and Treatment of Cancer; CUETO, the Spanish Urological Club for Oncological Treatment; BCG, bacillus Calmette–Guerin; TUR, transurethral resection; PSM, propensity score matching.

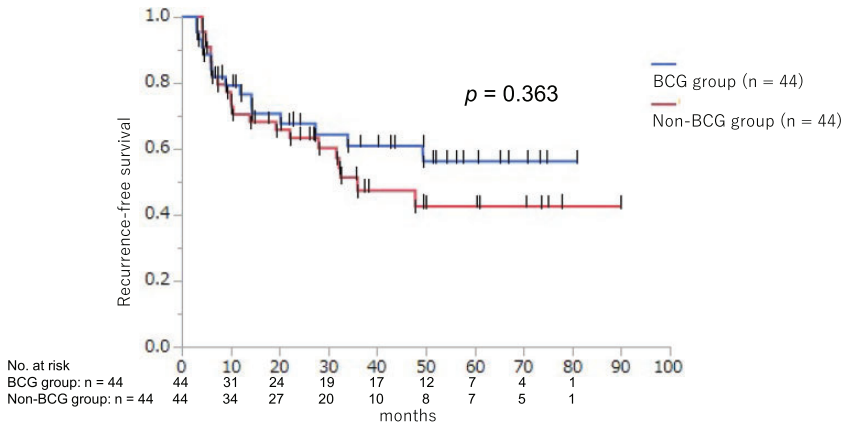
Follow-up period was expressed as the mean and (range), continuous variables with a normal distribution were reported as the mean SD, and categorical variables were reported as a number (percentage).

\*Independent-samples t-test or Student's t-test was used to compare the mean of two continuous normally distributed variables.

<sup>γ</sup>Chi-square test was used for categorical variables.



**Figure 4.** Recurrence-free survival of the non-intake (n=48) and intake (n=48) groups after PSM analysis PSM, propensity score matching



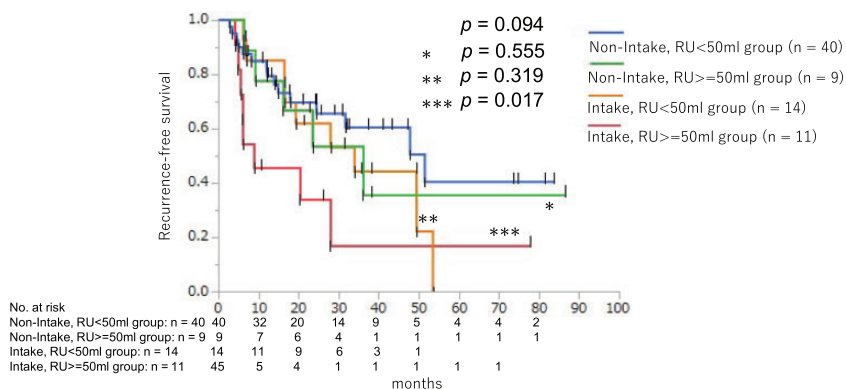
**Figure 5.** Recurrence-free survival of the BCG (n=44) and non-BCG (n=44) groups after PSM analysis BCG, bacillus Calmette–Guerin; PSM, propensity score matching.

**Table 4.** Dysuria agents used in the intake group

	Before PSM		After PSM	
	54 patients	Recurrent**	48 patients	Recurrent**
Number of patients (%)	54 (100.0)	36/54 (66.7)	48 (100.0)	32/48 (66.7)
Alpha-1 blocker	40 (74.1)	24/40 (60.0)	37 (77.1)	21/37 (56.8)
Cholinergic drug	6 (11.1)	4/6 (66.7)	6 (12.5)	4/6 (66.7)
Dutasteride	7 (13.2)	5/7 (71.4)	5 (10.4)	3/5 (60.0)
Herbs	15 (28.3)	10/15 (66.7)	12 (25.0)	9/12 (75.0)
Anti-androgen	3 (5.6)	3/3 (100.0)	3 (6.3)	3/3 (100.0)
Total	71 (131.5)*	46/71 (64.8)*	63 (131.3)*	40/63 (63.5)*

PSM, propensity score matching.

\*Including duplications, \*\*Excluding non-recurring cases after administration.



**Figure 6.** Differences in recurrence-free survival based on the intake status and RU. \* $p=0.017$  for the intake and residual urine  $\geq 50$  mL group versus the non-intake and residual urine  $< 50$  mL group RU, residual urine.

dysuria and BCG therapy were identified as statistically significant recurrence risk factors. It was not surprising that BCG therapy was associated with recurrence in the multivariate analysis because several reports have shown that intravesical BCG therapy inhibits the recurrence of medium- and high-risk NMIBC.<sup>14–16</sup> However, the identification of dysuria agent use as a candidate recurrence factor was surprising and difficult to interpret. Therefore, in this retrospective study, PSM analysis was used to investigate the robustness of these factors. In contrast to before PSM, BCG therapy was not significantly related to a longer RFS after PSM analysis. One explanation is that 15 patients who responded well to BCG therapy (recurrence rate 26.7%, 4/15 patients) were removed after PSM adjustment (Table 1, 3). This was because the treatments, including BCG therapy, showed selection bias depending on the malignancies. Moreover, our post-TURBT treatment plans and follow-up schedules were not stratified in accordance with the European Association of Urology guidelines. If we maintained the guidelines, the differences in RFS between the BCG and non-BCG groups might not have been significant. Therefore, it is considered

acceptable that there was no significant difference in the post-PSM study with a more consistent patient background. In contrast, because the use of dysuria agents did not depend on the grade of bladder cancer, a significant difference was maintained after PSM. Therefore, the use of agents for dysuria might be considered a new independent risk factor for recurrence, regardless of the existing risk factors.

The bladder temporarily stores and discharges urine, which is a metabolite produced through various reactions. One factor contributing to the onset and progression of bladder cancer is intraluminal dissemination, which is the seeding of cancer cells on the bladder wall via urine.<sup>17</sup> Partially supporting this idea, Matsumoto et al. reported that injecting carcinogens into the bladder of rats with LUTS induced bladder cancer, whereas carcinogen administration to rats without LUTS did not.<sup>18</sup> Only one clinical study has reported the association between LUTS and the risk of recurrence of NMIBC using the International Prostate Symptom Score (IPSS).<sup>19</sup> In this study, the presence of moderate or severe LUTS in men at the time of diagnosis was associated with increased recurrence rates of

NMIBC. Moreover, the  $p$ -value for benign prostatic hyperplasia medications between recurrence and non-recurrence groups was 0.09, indicating a slightly significant difference. The number of patients in their study was 70, and the statistical power was low.<sup>19</sup> However, in our study, the number of patients was 162. Therefore, our investigation might have more strongly reflected the impact of difficult urination symptoms in NMIBC.

Prognostic factors that have been reported for NMIBC include second TURBT,<sup>20–22</sup> female patients,<sup>23–25</sup> diabetes and neurogenic bladder.<sup>26,27</sup> There have been various reports on these factors; therefore, it was difficult to determine which factors affect the recurrence risk of NMIBC. As described above, we conducted PSM analysis to remove factors that displayed significant differences between the two groups regarding dysuria agents and BCG therapy. As a result, no factors showed a significant difference between the non-risk and risk groups after PSM analysis.

There are some limitations to this study. First, not all patients were evaluated for the micturition status at the time of the first appearance and during the follow-up period because past information could only be obtained from medical records. In addition, because it was a retrospective study, the observation periods were different for each patient. Second, therapeutic agents for dysuria are not a direct surrogate of the risk of bladder cancer recurrence. In this study, patients who did not recur after taking agents for dysuria were included in the intake group. Nagata et al. showed that the dysuria agent silodosin strongly inhibited both the carcinogen-mediated neoplastic transformation of adrenergic receptor (AR)-positive urothelial cells and the growth of AR-positive bladder cancer cells.<sup>28</sup> Third, the timing, selection and dosage of therapeutic agents for dysuria depended on the decision of each clinician.

Moreover, we could not exclude whether the therapeutic agent was used for improving urination difficulties because of urethral stricture, which is one complication following TURBT. Fourth, when each group was allocated by intake status for the four types of dysuria agents, the number of intake patients varied with each agent, as shown in Table 4. Among the intake groups, the number of cases treated with anti-androgens, cholinergic drugs and dutasteride were insufficient. Therefore, we did not investigate the recurrence status by dysuria agents. Additionally, recurrence investigations by comorbidities were not performed because of the small number of cases. Fifth, only two patients received an immediate epirubicin instillation following the primary TURBT in the non-intake group. There was no recurrence in these two patients. Sixth, throughout most of the follow-up period, 5-aminolevulinic acid had not yet been introduced for the TUR procedure. The recurrence rate may change in the future after using this innovative treatment.<sup>29–31</sup> Finally, because the number of patients was small, and it was a retrospective study, this study was underpowered to show any statistical significance. In the future, a larger prospective study should be conducted.

## Conclusions

This study demonstrated that patients with voiding symptoms requiring oral administration of a therapeutic agent exhibited a significantly higher risk of recurrence than those without these symptoms. In the future, an accurate assessment of micturition function before and after bladder cancer treatment is necessary to show a direct association between urinary function and bladder cancer recurrence. To demonstrate this, it is necessary to evaluate not only urinary function, residual urine and IPSS in the patients with NMIBC but also

the difference in the quantification of carcinogenic substances in the urine.

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The authors declare that there is no conflict of interest.

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### Author contributions

YK: project development, data collection and management, data analysis and manuscript writing. DI, DK, MT, SK, AI, DT, TM, SM and JS: data collection. DI, RK, MK and RT: data collection and management. WO: project development, data analysis and manuscript editing.

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