

Recurrence of Low-risk Non-muscle-invasive Bladder Cancer in Patients Who Did Not Receive Immediate Intravesical Chemotherapy

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Abstract

Background/Aim: To reduce recurrence, immediate postoperative intravesical chemotherapy (IVC) is recommended for patients with low-risk non-muscle-invasive bladder cancer (NMIBC). This study evaluated recurrence outcomes in patients with low-risk NMIBC who did not receive immediate IVC and the potential benefit of introducing this approach. **Patients and Methods:** We retrospectively analyzed 100 patients with low-risk NMIBC who were selected from 1,845 patients who underwent transurethral resection of bladder tumor at our institution. According to international guidelines, low-risk was defined as primary, single, solitary (<3 cm), pTa, low-grade tumors without concomitant carcinoma *in situ*. None of the patients received immediate IVC. Tumors were re-evaluated using the 1973 and 2004/2016 World Health Organization classifications. Recurrence rates and patterns and oncological outcomes were examined.

Results: During a median follow-up of 69 months, 45 (45%) patients experienced recurrence. The cumulative recurrence rates were 21.6% at 1 year and 46.1% at 5 years. At first recurrence, high-grade progression was observed in 12% of the patients and upstaging to pT1 in 4%. Subsequently, 2% of patients progressed to muscle-invasive disease. The 5-year recurrence rates were 38.0% and 51.6% in G1 and G2 patients, respectively ($p=0.204$). The 5-year cancer-specific and overall survival rates were 98.3% and 89.4%, respectively.

Conclusion: The recurrence rate was high in low-risk patients with NMIBC who did not receive immediate IVC, and a subset of patients progressed to more aggressive disease. These findings underscore the potential benefit of introducing immediate IVC in this population.

Keywords: Non-muscle-invasive bladder cancer, intravesical chemotherapy, recurrence, immediate instillation, transurethral resection of bladder tumor.



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Introduction

Bladder cancer was the eighth most commonly diagnosed malignancy worldwide in 2022, with approximately 614,000 new recorded cases, 34,000 of which occurred in Japan (1). Among these cases, approximately 75% were initially diagnosed with non-muscle-invasive bladder cancer (NMIBC) (2). Generally, NMIBC has a favorable prognosis. However, it is characterized by a high recurrence rate, with 15%-61% of patients experiencing recurrence within 1 year and 31%-78% within 5 years after transurethral resection of bladder tumor (TURBT) (3-5).

To reduce recurrence risk, the European Association of Urology, American Urological Association, and Japanese Urological Association strongly recommend a single, immediate postoperative instillation of intravesical chemotherapy (IVC) after TURBT in patients with low-risk NMIBC (6-8). However, real-world adherence to this practice remains suboptimal. A systematic review published in 2020, which included 1,193 patients across 6 studies, reported a compliance rate of 53% for a single, immediate IVC after TURBT (9). In the Asia-Pacific region, a physician survey by Ku *et al.* found that 64% of respondents reported using immediate IVC within 24 h. Nevertheless, this finding was derived from self-reported practices and might not reflect actual implementation rates (10).

In Japan, national-level data on immediate IVC uptake are limited. Nevertheless, several operational barriers, including logistical challenges in postoperative drug preparation, limited staffing, safety concerns, and insufficient training or awareness among junior physicians, contribute to its underutilization.

At our institution, immediate IVC after TURBT has not been routinely implemented in patients with low-risk NMIBC. Considering this context, the current study aimed to evaluate the potential clinical value of introducing IVC by retrospectively analyzing recurrence rates and oncological outcomes in low-risk patients with NMIBC who did not receive immediate IVC.

Patients and Methods

Study design and patient selection. This retrospective, single-institutional study was conducted at the University of Occupational and Environmental Health (UOEH), Japan. The study protocol was approved by the institutional review board of UOEH (approval no.: UOEHCRB20-134). Considering that the study had a retrospective design, the requirement for a written informed consent was waived, with an opt-out option provided in the hospital's website.

According to international guidelines, low-risk was defined as primary, single, solitary (<3 cm), pTa, low-grade tumors without concomitant carcinoma *in situ* (CIS) (6-8). We reviewed 1,845 consecutive patients with bladder cancer who underwent TURBT between March 2005 and August 2020. Patients with recurrent disease (n=622), muscle-invasive bladder cancer (n=187), or metastatic disease (n=46) were excluded from the analysis. Of the remaining 990 patients with NMIBC, those with intermediate- or high-risk disease (n=738), non-urothelial histology (n=3), or missing important data (n=72) were further omitted. Among the 177 patients with low-risk NMIBC, 77 who received delayed IVC, which is beyond 24 h after TURBT, were additionally excluded.

The final cohort included patients who met the low-risk NMIBC criteria but did not receive immediate IVC. Figure 1 shows the patient selection process.

Pathological evaluation. The initial histopathological diagnoses were made by institutionally dedicated pathologists at the time of TURBT. Subsequently, all specimens were re-evaluated using both the 1973 World Health Organization (WHO) classification (G1-G3) and the 2004/2016 WHO classification (low or high grade) (11). Accordingly, certain tumors initially classified as G2 were included in the low-grade category because they met the histological criteria for low-grade urothelial carcinoma. These grading systems were also used in the recurrence analyses.

Follow-up and outcome measures. The postoperative surveillance included cystoscopy and urine cytology

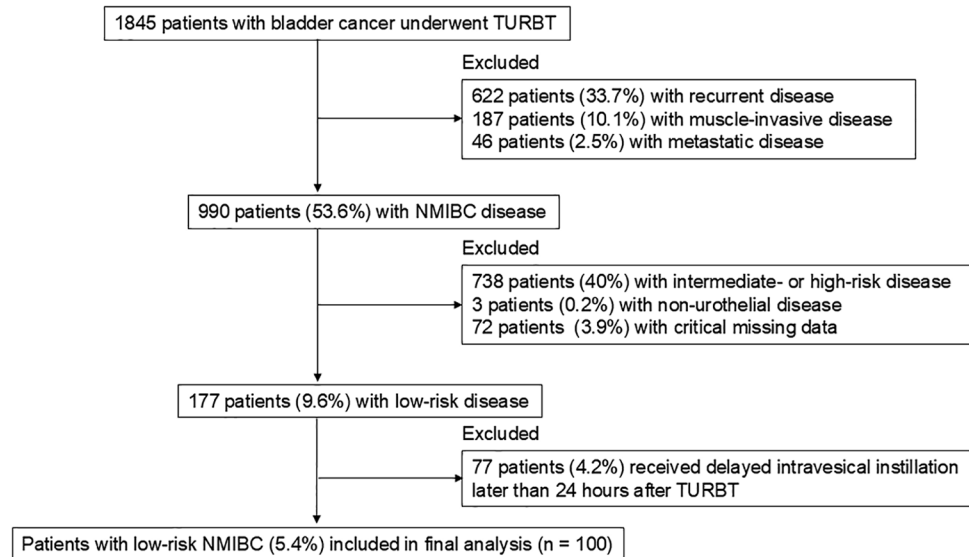


Figure 1. Patient selection flowchart for initial low-risk NMIBC. TURBT: Transurethral resection of bladder tumor; NMIBC: non-muscle-invasive bladder cancer.

every 3 months within the first 2 years and every 6 months thereafter. Recurrence was defined as the histologically confirmed return of bladder tumor, including CIS. Cumulative recurrence was analyzed from the date of initial TURBT to the date of the first documented recurrence. In addition, recurrence rates and patterns were compared between G1 and G2 tumors based on the 1973 WHO grading system (11). Moreover, cancer-specific survival (CSS) was defined as the time from TURBT to death attributed to bladder cancer. Overall survival (OS) was defined as the time from TURBT to death from any cause or to the last follow-up in patients who survived.

Statistical analysis. Categorical variables were compared using the Fisher's exact test. Cumulative recurrence, CSS, and OS were examined using the Kaplan–Meier method. Between-group differences were assessed using the log-rank test. Intergroup differences in the number of tumor recurrences were evaluated using the Mann–Whitney *U*-test, with consideration of the nonparametric nature of the data. A two-sided *p*-value of <0.05 was considered statistically significant. All statistical analyses were

performed using EZR version 1.55 (Easy R, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (12).

Results

Characteristics of the patients. Of the 1,845 patients who underwent TURBT, 100 (5.4%) met the criteria for low-risk NMIBC, and they did not receive immediate IVC. These patients were included in the analysis. Table I shows the baseline characteristics of the patients. The median age of the participants was 73 [interquartile range (IQR)=66-79] years, and 77% were men. All tumors were low-grade, and 41 (41%) and 59 (59%) were classified as G1 and G2, respectively, based on the 1973 WHO classification (11). None of the patients received immediate or delayed IVC after TURBT.

Recurrence outcomes. Over a median follow-up period of 69 (IQR=46-114) months, 45 (45%) patients developed tumor recurrence. The cumulative recurrence rates were 21.6% at 1 year, 33.9% at 2 years, and 46.1% at 5 years (Figure 2). Among those with recurrence, 12 (12%)

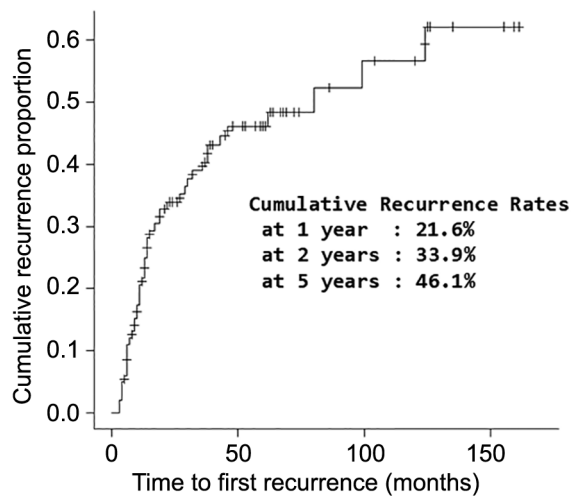


Figure 2. Cumulative recurrence rates after TURBT in patients with low-risk NMIBC. TURBT: Transurethral resection of bladder tumor; NMIBC: non-muscle-invasive bladder cancer.

patients presented with high-grade progression and 4 (4%) with upstaging to pT1 (Table I). No cases of muscle-invasive bladder cancer were observed at the time of first recurrence; subsequent progression occurred in two cases.

Subgroup analysis: G1 versus G2. When stratified by tumor grade based on the 1973 WHO classification, the 5-year cumulative recurrence rates were 38.0% in G1 tumors and 51.6% in G2 tumors. Although recurrence was more frequent in G2 than in G1 tumors, the difference was not statistically significant ($p=0.204$, Figure 3).

The patterns of initial recurrence also differed between the two groups (Table II). High-grade progression was observed in 37.5% (6/16) of patients with G1 tumors and 20.7% (6/29) of those with G2 tumors. Upstaging to pT1 occurred in 18.8% (3/16) of patients with G1 tumors and in 3.4% (1/29) of those with G2 tumors. Recurrent tumors were also more likely to be multifocal in the G2 group.

Further, patients with G2 tumors had a significantly higher total number of recurrences per patient than those with G1 tumors (median=2 vs. 1), as shown in Figure 4 ($p=0.045$).

Table I. Baseline characteristics of patients with low-risk NMIBC.

Characteristics	N=100
Median age, years (IQR)	73 (66-79)
Sex, n (%)	
Male	77 (77)
Female	23 (23)
Tumor grade (WHO 1973), n (%)	
1	41 (41)
2	59 (59)
Recurrence, n (%)	
No	55 (55)
Yes	45 (45)
Upstaging to pT1 at first recurrence, n (%)	4 (4)
Upgrading to high grade at first recurrence, n (%)	12 (12)
MIBC at first recurrence, n (%)	0 (0)
Survival status at the last follow-up, n (%)	
Alive	81 (81)
Deceased due to bladder cancer	2 (2)
Deceased due to other causes	17 (17)
Median follow-up duration, months (IQR)	69 (46-114)

IQR: Interquartile range; MIBC: muscle-invasive bladder cancer; pT1: pathological T1; NMIBC: non-muscle-invasive bladder cancer.

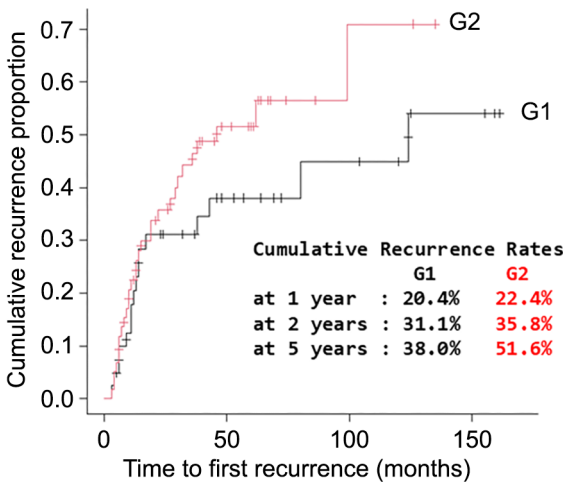


Figure 3. Comparison of cumulative recurrence rates between G1 and G2 tumors in low-risk NMIBC. NMIBC: Non-muscle-invasive bladder cancer.

Survival outcomes. Figure 5 depicts the Kaplan–Meier survival curves for CSS and OS. At 5 years, the CSS and OS rates were 98.3% and 89.4%, respectively. The corresponding 10-year rates were 98.3% for CSS and 72.9% for OS. During the follow-up period, there were 19

Table II. Patterns of first recurrence stratified by initial tumor grade in patients with low-risk NMIBC.

Characteristics	Patients with G1 tumors (n=16)	Patients with G2 tumors (n=29)	p-Value
Upstaging to pT1			0.121
No	13 (81.2)	28 (96.6)	
Yes	3 (18.8)	1 (3.4)	
Upgrading to high grade			0.296
No	10 (62.5)	23 (79.3)	
Yes	6 (37.5)	6 (20.7)	
Presence of CIS			0.455
No	11 (68.8)	24 (82.8)	
Yes	5 (31.2)	5 (17.2)	
Multiple tumors			0.542
No	9 (56.2)	13 (44.8)	
Yes	7 (43.8)	16 (55.2)	

pT1: Pathological T1; CIS: carcinoma *in situ*; NMIBC: non-muscle-invasive bladder cancer. Note: all values are presented as n (%).

deaths, including 2 attributed to bladder cancer and 17 due to other causes. Considering the limited number of cancer-related deaths, survival outcomes were not statistically compared between G1 and G2 tumors.

Discussion

This study aimed to evaluate recurrence outcomes in patients with low-risk NMIBC who did not receive IVC. Despite meeting the low-risk criteria according to international guidelines (6-8), nearly half of the patients experienced recurrence over a median follow-up of 69 months. Further, 12% of the patients presented with high-grade transformation at first recurrence and 4% with upstaging to pT1. The steep recurrence curve within the first 2 years (33.9%) further underscores the importance of early disease control.

These findings indicate that even tumors classified as low-risk have a clinically significant risk of recurrence and disease progression in the absence of immediate IVC. Although the benefits of immediate IVC are well established (13, 14), its implementation remains inconsistent across institutions. Our data provide a real-world insight into the consequences of omitting this intervention and support its broader adoption in clinical practice.

The 5-year recurrence rate in our cohort was comparable to that reported in the TURBT-alone arm of a

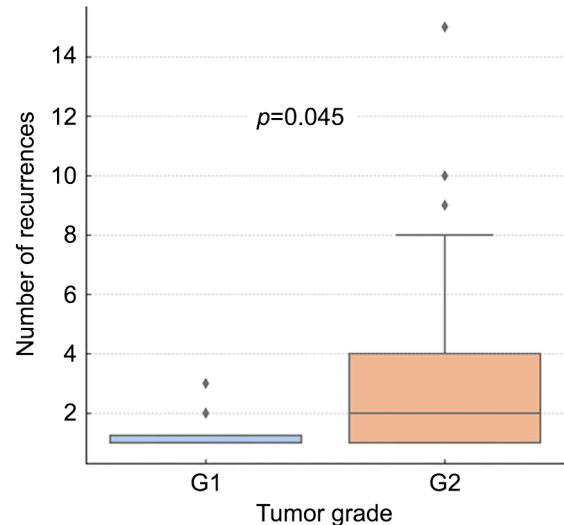


Figure 4. Number of tumor recurrences according to initial tumor grade among patients with low-risk NMIBC. The boxes represent interquartile ranges, the horizontal lines within the boxes indicate medians, and the whiskers show the range excluding outliers. Outliers are plotted as individual points. Statistical comparison was performed using the Mann-Whitney U-test. NMIBC: Non-muscle-invasive bladder cancer.

meta-analysis by Sylvester *et al.* (46.1% vs. 48.4%) (13). All tumors were initially low-grade. However, histological progression was common at the time of recurrence, with some cases exhibiting high-grade features, CIS, or stage migration. Among patients with G1 tumors who experienced recurrence, approximately one-third developed high-grade components, thereby indicating the

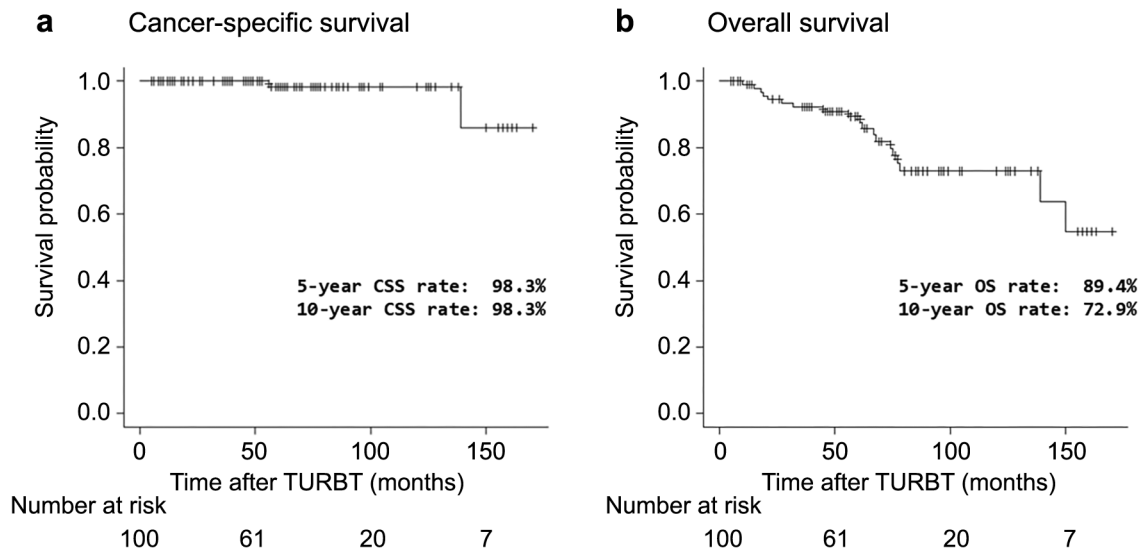


Figure 5. Kaplan–Meier survival curves of patients with low-risk NMIBC: (a) cancer-specific survival, (b) overall survival. NMIBC: Non-muscle-invasive bladder cancer; CSS: cancer-specific survival; OS: overall survival.

potential for biological evolution even in lesions initially considered indolent. Similarly, Kirkali *et al.* reported grade progression in up to 20% of recurrent low-grade tumors (15). Kobayashi *et al.* revealed that Japanese patients with recurrent TaG1 disease had worsening pathological features during long-term follow-up (5). Our results reconfirm these findings and challenge the notion that G1 tumors are biologically inert.

A comprehensive meta-analysis showed that a single IVC within 24 h post-TURBT reduced the risk of recurrence by 35% compared to TURBT-alone (14). In addition, it not only delays the time to first recurrence but also reduces the total number of recurrences over time (16). Several agents, including mitomycin C, epirubicin, pirarubicin, and gemcitabine, have been used for immediate IVC (17–20). Among these agents, mitomycin C and epirubicin have been traditionally supported by substantial evidence from Western clinical trials (21). Meanwhile, the use of gemcitabine has recently gained strong support from randomized trials and meta-analyses showing that it has superior efficacy and safety compared with mitomycin C (20, 22). In contrast, pirarubicin is widely used in Japan owing to its favorable safety profile and short dwell time in

the bladder (10, 19). Moreover, no additional therapy prior to recurrence is recommended for low-risk patients (23).

Although our study was not primarily designed to compare G1 and G2 tumors, the observed recurrence patterns indicate that tumor grade, even within the low-grade category, reflects a biologically heterogeneous entity. G2 tumors are more likely to follow a more consistent recurrence course. Meanwhile, G1 tumors exhibit more variable recurrence patterns, including tendencies toward grade progression and the presence of CIS. These subtle but significant differences in tumor behavior may become increasingly clear over time, particularly in the absence of IVC. This finding might support the clinical relevance of incorporating histological grade into risk-adapted surveillance strategies, even within low-risk NMIBC.

Low-risk NMIBC rarely leads to bladder cancer-specific mortality if patients are monitored appropriately (2). Nevertheless, recurrence remains clinically significant. In our cohort, recurrence and progression did not compromise the 5-year CSS. However, they imposed a substantial burden. Repeated TURBT procedures, surveillance cystoscopy, and recurrence-related anxiety

remarkably affect patients' quality of life and healthcare costs (24, 25). This contrast between excellent survival and frequent recurrence reinforces an important clinical message: low-risk does not indicate no risk.

Study limitations. First, it had a retrospective, single-center design, which might have limited the generalizability of our findings. However, all patients were treated and followed according to a uniform institutional protocol, which minimized treatment heterogeneity. Second, pathological grading was not centrally reviewed, thereby introducing potential interobserver variability despite institutional consistency. Nonetheless, all pathological evaluations were performed by board-certified uropathologists within the same department, ensuring internal consistency. Statistical analyses were conducted using appropriate non-parametric methods (Mann–Whitney *U* and log-rank tests) to account for data distribution and sample size limitations. Third, the lack of a comparator group for immediate postoperative IVC precludes direct quantification of its preventive efficacy.

Nevertheless, the uniform exclusion of immediate IVC in this cohort, while providing a homogeneous treatment context, represents a distinct clinical setting that may not reflect broader practice patterns. Although this approach was not originally intended, it allowed for an unfiltered observational view of the natural course of low-risk NMIBC without adjuvant intervention. In that sense, our findings can be a real-world cautionary reminder: even low-risk tumors based on international guidelines can pose a substantial recurrence burden when IVC is omitted.

Beyond the current findings, advances in diagnostic technology are expected to further refine the management of low-risk NMIBC. Photodynamic diagnosis using 5-aminolevulinic acid (5-ALA) has recently gained attention for its ability to enhance the visualization of residual or multifocal lesions that might be overlooked under conventional white-light cystoscopy (26, 27). Additionally, in cases where IVC is not performed, continuous saline bladder irrigation may serve as an

alternative approach to reduce the risk of tumor recurrence (28). As these techniques become more widely available, their diagnostic value in risk stratification and postoperative management will likely increase, complementing the preventive role of immediate IVC.

Low-grade Ta tumors are often categorized collectively as low-risk NMIBC in current clinical practice. Thus, future prospective studies must be carried out to validate whether histologic subclassification – such as distinguishing G1 from G2 tumors – can be used as a guide for individualized surveillance or adjuvant strategies, particularly in IVC-naïve settings. Further, the integration of molecular or urinary biomarkers may enhance risk prediction and inform precision-based follow-up. Ultimately, bridging prognostic insights with practical clinical algorithms will be a key to optimizing the management of low-risk NMIBC.

Conclusion

Even low-risk NMIBC can exhibit clinically significant recurrence in the absence of immediate IVC. These results emphasize the potential value of immediate IVC in routine clinical practice, highlighting the need for further prospective studies to determine the optimal intravesical agent.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

AM: Conceptualization, investigation, data curation, formal analysis, and writing of the original manuscript. KJ, SW, YS, YM, TM, RK, KH and YN: Investigation and data curation. IT: Reviewing of the manuscript. EK: Conceptualization and reviewing of the manuscript. All Authors discussed, verified, and approved the final version of the article.

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Artificial Intelligence Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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