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# Poor Prognosis With Intravesical Bacillus Calmette-Guérin History After Photodynamic Diagnosis-assisted Transurethral Resection Using 5-Aminolevulinic Acid

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**Abstract.** *Background/Aim: Diagnostic efficacy and treatment outcome of orally administered 5 aminolevulinic acid (ALA) assessment for photodynamic diagnosis (PDD) in transurethral resection for non-muscle-invasive bladder cancer (NMIBC) in clinical practice. Patients and Methods: A retrospective analysis was performed of 105 patients who underwent PDD transurethral resection using orally administered ALA and were pathologically diagnosed with Ta, T1, or Tis at the Ishikawa Prefectural Central Hospital from December 2018 to May 2022. Results: Fluorescent light had a significantly higher sensitivity but a lower specificity in detecting carcinoma compared to white light (91.7% vs. 77.1%; p<0.05 and 43.0% vs. 85.2%; p<0.05, respectively), as well as in detecting carcinoma in situ lesions (80.4% vs. 28.6%; p<0.05 and 23.3% vs. 84.5%; p<0.05, respectively). The cumulative frequency of recurrence and progression 1 year after treatment were 26.3% and 12.3%, respectively. Multivariate analyses indicated that a Bacillus Calmette-Guérin (BCG) history instillation was an independent predictive factor for intravesical recurrence (hazard ratio=4.439; p=0.002) and disease progression (hazard ratio=8.534; p=0.005). The 1-year cumulative recurrence rates were 66.2% and 16.5%, respectively (p<0.001), and progression rates for patients with and without prior BCG intravesical instillation were 50.4% and 3.5%, respectively (p<0.001). Conclusion: Sufficient diagnostic accuracy and relatively good treatment outcome was shown in PDD-transurethral resection using ALA. However, prior BCG intravesical instillation for NMIBC patients was a poor prognostic factor of cancer recurrence and progression, and may be useful for clinicians in their postoperative follow-up.*

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*Key Words:* 5-aminolevulinic acid, photodynamic diagnosis, fluorescence, transurethral resection, bladder cancer, urothelial carcinoma, Bacillus Calmette-Guérin.



Transurethral resection of bladder tumor (TURBT) by intraoperative cancer detection under white light (WL) (1) is the standard therapy for non-muscle-invasive bladder cancer (NMIBC) in clinical practice, which accounts for approximately 70% of bladder cancers (BCs). However, about 50% of NMIBCs recur, and BC invades the muscle layer in the recurrence process in 15%-30% of cases (2). Therefore, improving TURBT quality and increasing the complete tumor resection rate is essential to reduce the recurrence risk. The protoporphyrin IX precursor called 5-aminolevulinic acid (ALA) is attracting attention as a new generation photosensitive material for photodynamic diagnosis (PDD). PDD assisted TURBT using orally administered ALA has demonstrated clear advantages in Japan in terms of increased tumor detection and improved oncological outcome (3-7). Clinical data originating from Japan are not yet sufficient, although ALA was made available under the Japanese public medical insurance system in 2017.

Recently, the Bacillus Calmette-Guérin (BCG) unresponsive disease concept was advocated; a group of diseases that recur despite adequate BCG intravesical therapy and are considered ineffective for reintroduction of BCG intravesical therapy (8, 9). However, it is unclear how prior BCG intravesical treatment affects outcomes after TURBT for NMIBC in the PDD era.

Hence, this study aimed to determine the diagnostic accuracy of PDD-assisted TURBT using ALA in real

Table I. *Patient characteristics*.

| | N=105 |
|---|---|
| Age, years, median (IQR) | 72 (69-77) |
| Sex | |
| Male | 88 (83.8) |
| Female | 17 (16.2) |
| Past history | |
| Primary case | 59 (56.2) |
| Recurrence case | 46 (43.8) |
| Preoperative cytology | |
| Positive | 55 (52.4) |
| Negative | 47 (44.8) |
| Not available | 3 (2.8) |
| Prior BCG therapy | 17 (16.2) |
| Operation time, min, median (IQR) | 36 (23-52) |
| Adjuvant instillation | |
| Immediate single instillation with THP | 78 (74.3) |
| THP maintenance | 26 (24.8) |
| BCG | 48 (45.7) |
| None | 31 (29.5) |

IQR: Interquartile range; BCG: Bacillus Calmette-Guérin; THP: pirarubicin. Data presented as n (%), unless otherwise noted.

Table II. *Oncological findings*.

| | N=105 |
|---|---|
| Multiplicity | |
| Single | 50 (47.6) |
| Multiple | 55 (52.4) |
| Tumor size | |
| <1 cm | 32 (30.5) |
| 1-3 cm | 47 (44.8) |
| ≥3 cm | 3 (2.9) |
| Unknown | 23 (21.9) |
| Pathological T stage | |
| Ta | 58 (55.2) |
| T1 | 24 (22.9) |
| Tis | 12 (11.4) |
| Ta+Tis | 7 (6.7) |
| T1+Tis | 4 (3.8) |
| Grade | |
| Low | 23 (21.9) |
| High | 69 (65.7) |
| Unknown | 13 (12.4) |
| EAU risk classification | |
| Low | 12 (11.4) |
| Intermediate | 32 (30.5) |
| High | 50 (47.6) |
| Very high | 7 (6.7) |
| Unknown | 4 (3.8) |

EAU: European Association of Urology. Data presented as n (%).

clinical practice, and to retrospectively identify prognostic factors for predicting recurrence and progression after PDD-assisted TURBT.

## Patients and Methods

*Patients*. A total of 130 patients underwent PDD-TURBT using orally administered ALA at the Ishikawa Prefectural Central Hospital from December 2018 to May 2022. Of these, 105 patients pathologically diagnosed with Ta, T1, or Tis BC were included in this retrospective study. The Medical Ethics Committee of Ishikawa Prefectural Central Hospital approved this study.

*Data collection and variable definitions*. The patients' clinical characteristics including age, sex, previous recurrence status, positive preoperative urinary cytology presence, BCG intravesical infusion therapy history, and postoperative intravesical infusion therapies were retrospectively reviewed, as shown in Table I. The oncological variables were assessed according to a web-based calculator (10), including tumor size and multiplicity, pathological T stage, tumor grade, and European Association of Urology (EAU) prognostic factor risk classification (11). The Common Terminology Criteria for Adverse Events v5.0 was used to assess ALA-related adverse events.

Cumulative intravesical recurrence and progression were defined as the time from the initial transurethral resection day to the first intravesical recurrence, and the time from the appearance of bladder muscle layer invasion or metastasis, respectively.

*Surgical procedure*. ALA (ALAGLIO®; SBI Pharmaceuticals, Tokyo, Japan) was diluted in 50 ml of water and administered orally at 20 mg/kg, usually 3 h (range=2-4 h) before surgery in clinical practice. Cystoscopic observation and tissue collection were alternately performed under a WL and fluorescent light (FL) source. A Storz D-LIGHT C/AF System (KARL STORZ GmbH, Tuttlingen, Germany) and an IMAGE1 S™ Camera Systems (KARL STORZ GmbH) were used to carry out PDD assistance during surgery.

*Protocol for follow-up after TURBT*. Whether adjuvant intravesical infusion therapies were performed depended on the judgment of the individual physician based on pathological results after TURBT. Postoperative follow-up protocols included cystoscopy and urine cytology every 3-6 months at the individual physician's discretion.

*Diagnostic accuracy in PDD-TURBT*. PDD-TURBT's diagnostic accuracy was examined by comparing endoscopic findings according to WL or FL with pathology results, and determining the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in accordance with previous reports (12).

*Statistical analyses*. Significant differences between WL and FL were determined by McNemar's test for sensitivity and specificity, and by chi-square test for PPV and NPV. The Kaplan-Meier method was used to calculate the cumulative intravesical recurrence and progression rates and statistically compared using the log-rank test. The Cox proportional hazards models were used to perform the univariate and multivariate analyses to evaluate the prognostic variables affecting recurrence and progression. The GraphPad Prism version 6.07 (GraphPad Software Inc., San Diego, CA, USA) and IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) were used to perform statistical analyses. Statistical significance was defined as a $p$-value <0.05.

Table III. *White light and fluorescent light diagnostic accuracy in all 327 specimens.*

| | WL(+) or FL(+)/total positive lesion | Sensitivity (%) (95%CI) | WL(−) or FL(−)/ total negative lesion | Specificity (%) (95%CI) | Positive lesion/ WL(+) or FL(+) | Positive predictive value (%) (95%CI) | Negative lesion/ WL(−) or FL(−) | Negative predictive value (%) (95%CI) |
|---|---|---|---|---|---|---|---|---|
| WL (All tumor) | 148/192 | 77.1 (70.5-82.8) | 115/135 | 85.2 (78.1-90.7) | 148/168 | 88.1 (82.2-92.6) | 115/159 | 72.3 (64.7-79.1) |
| FL (All tumor) | 176/192 | 91.7 (86.8-95.2) | 58/135 | 43.0 (34.5-51.8) | 176/253 | 69.6 (63.5-75.2) | 58/74 | 78.4 (67.3-87.1) |
| *p*-Value | | $p<0.05$ | | $p<0.05$ | | $p<0.05$ | | $p=0.33$ |
| WL (CIS) | 16/56 | 28.6 (17.3-42.2) | 229/271 | 84.5 (79.6-88.6) | 16/58 | 27.6 (16.7-40.9) | 229/269 | 85.1 (80.3-89.2) |
| FL (CIS) | 45/56 | 80.4 (67.6-89.8) | 63/271 | 23.3 (18.4-28.7) | 45/253 | 17.8 (13.3-23.1) | 63/74 | 85.1 (75.0-92.3) |
| *p*-Value | | $p<0.05$ | | $p<0.05$ | | $p=0.09$ | | $p=0.99$ |

WL: White light; FL: fluorescent light; CIS: carcinoma in situ; CI: confidence interval. All lesions were included in the analysis of diagnostic accuracy of WL and FL. Positive and negative lesions indicate histological classification as tumor-positive and -negative, respectively.

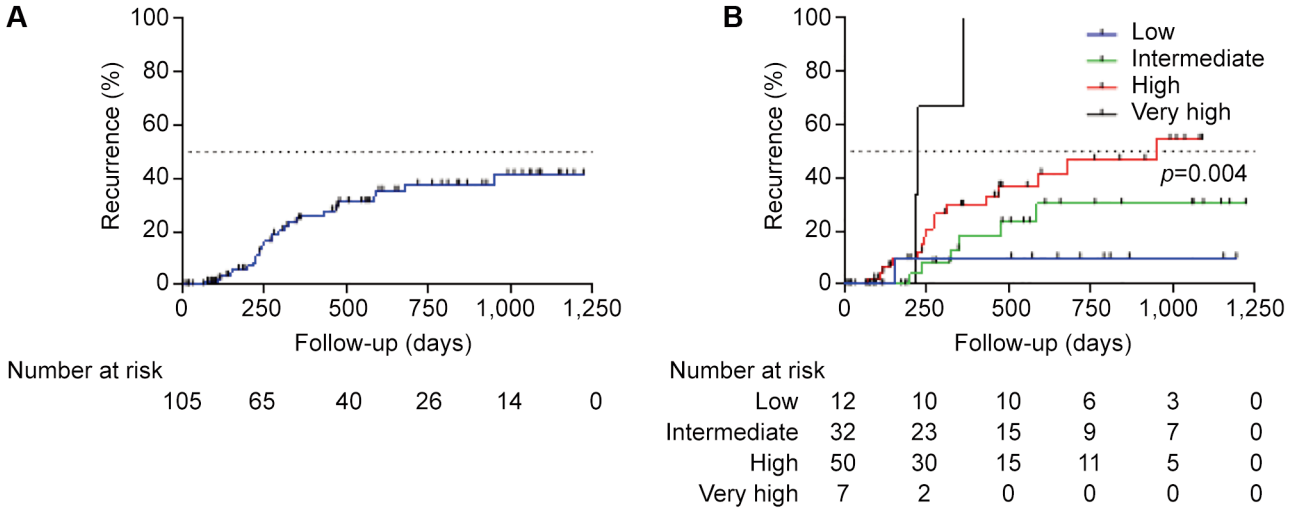


Figure 1. *Kaplan-Meier analyses for time to recurrence in (A) overall patients and (B) patients stratified by the European Association of Urology risk classification.*

## Results

*Clinical and oncological findings.* This study included 327 total specimens from 105 patients. The median follow up period was 365 days [interquartile range (IQR)=174-719 days]. Table II shows the clinicopathological outcomes. The median tumor size was 1.0 cm (IQR=0.5-1.5 cm). Of the 105 patients, 58 (55.2%), 24 (22.9%), 12 (11.4%), 7 (6.7%), and 4 (3.8%) were in pathological stage Ta, T1, Tis, Ta+Tis, and T1+Tis, respectively. Tumor grade was low grade in 23 patients (21.9%), high grade in 69 (65.7%), and unknown in 13 (12.4%). According to the EAU risk classification, 12 patients (11.4%) were at low-risk, 32 (30.5%) were at intermediate-risk, 50 (47.6%) were at high-risk, 7 (6.7%) were at very high-risk, and 4 (3.8%) were unknown, respectively. Prior intravesical BCG treatment was administered in 17 patients (16.2%) and complete resection was achieved in 92 patients (87.6%).

*FL and WL efficacy for total lesions and carcinoma in situ lesions.* The sensitivity, specificity, PPV, and NPV for detecting urothelial carcinoma were 77.1% [95% confidence interval (CI)=70.5-82.8%], 85.2% (95%CI=78.1-90.7%), 88.1% (95%CI=82.2-92.6%), and 72.3% (95%CI=64.7-79.1%) for WL, and 91.7% (95% CI=86.8-95.2%), 43.0% (95%CI=34.5-51.8%), 69.6% (95%CI=63.5-75.2%), and 78.4% (95%CI=67.3-87.1%) for FL, respectively. In contrast, for detecting carcinoma *in situ* (CIS) lesions, WL

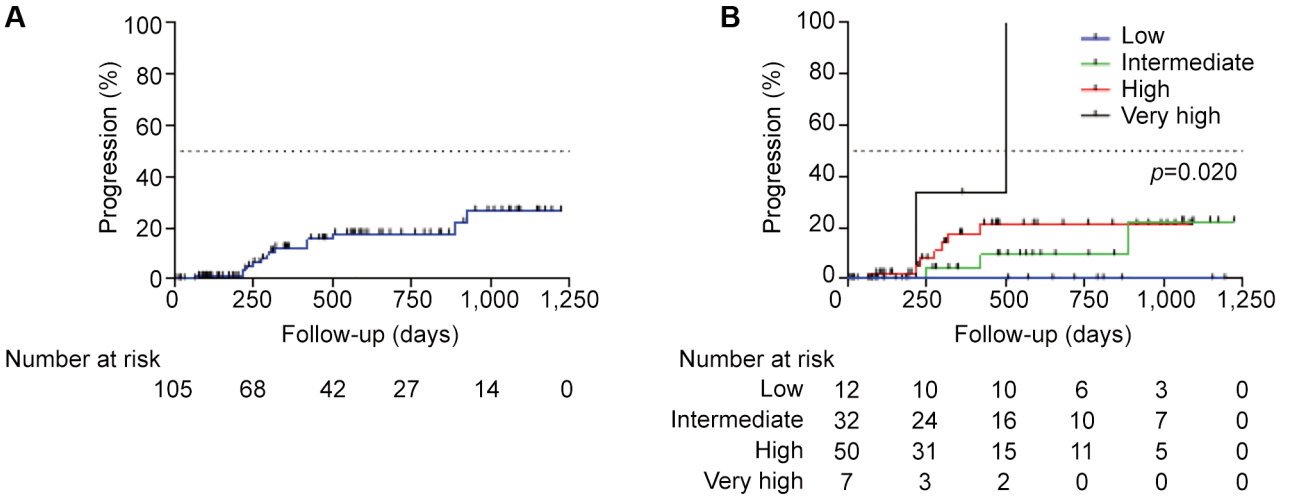


Figure 2. *Kaplan-Meier analyses for time to progression in (A) overall patients and (B) patients stratified by the European Association of Urology risk classification.*

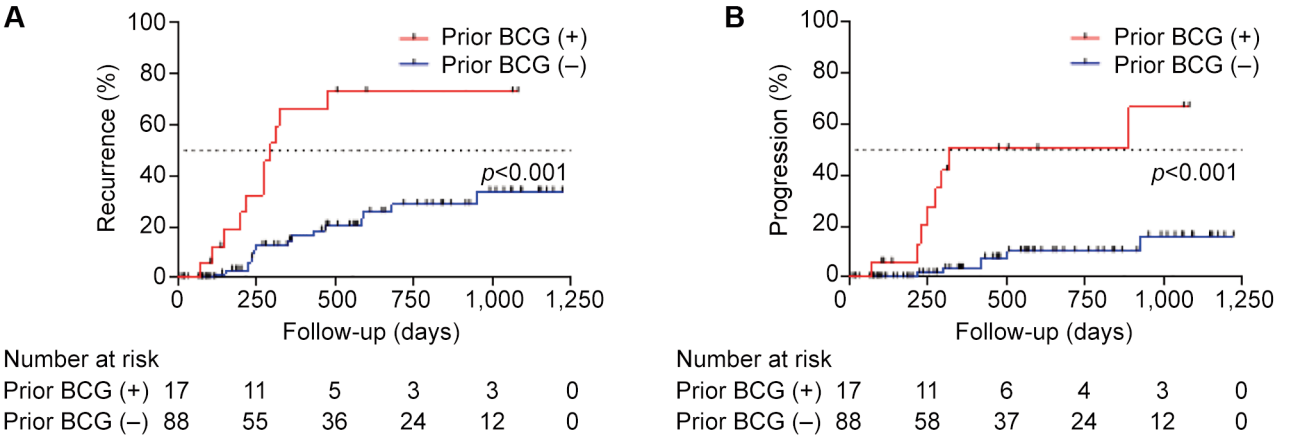


Figure 3. *Kaplan-Meier analyses for time to (A) recurrence and (B) progression in patients with and without prior Bacillus Calmette-Guérin intravesical instillation.*

and FL had a sensitivity of 28.6% (95%CI=17.3-42.2%) and 80.4% (95%CI=67.6-89.8%), specificity of 84.5% (95%CI=79.6-88.6%) and 23.3% (95%CI=18.4-28.7%), PPV of 27.6% (95% CI=16.7-40.9%) and 17.8% (95%CI=13.3-23.1%), and NPV of 85.1% (95%CI=80.3-89.2%) and 85.1% (95%CI=75.0-92.3%), respectively. FL had a significantly higher sensitivity but lower specificity for detecting carcinoma as well as CIS lesions compared to WL ($p<0.05$, Table III).

*Survival rates and prognostic factor.* Of the 105 patients, 27 (25.7%) had tumor recurrence and 14 (13.3%) developed MIBC or distant metastasis. The recurrence proportion 1 year after treatment was 26.3% (Figure 1A), and 1-year cumulative recurrence rates for low-, intermediate-, high-, and very high-risk patients according to the EAU risk classification were 10.0%, 18.3%, 29.7%, and 100%, respectively ($p=0.004$; Figure 1B). Progression 1 year after treatment was 12.3% (Figure 2A), and the 1-year cumulative progression rates for low-, intermediate-, high-, and very high-risk patients were 0%, 4.2%, 17.7%, and 33.3%, respectively ($p=0.020$; Figure 2B). Multivariate analysis demonstrated that a BCG instillation history was independently associated with intravesical recurrence [hazard ratio (HR)=4.439; 95%CI=1.725-11.422; $p=0.002$] as well as disease progression (HR=8.534; 95%CI=1.898-38.370;

Table IV. *Prognostic variables for intravesical recurrence and disease progression.*

| Variables | Recurrence | | | | Progression | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate | | Multivariate | | Univariate | | Multivariate | |
| | *p*-Value | HR (95%CI) | *p*-Value | HR (95%CI) | *p*-Value | HR (95%CI) | *p*-Value | HR (95%CI) |
| Age† | 0.087 | 1.048 (0.993-1.105) | | | 0.010 | 1.112 (1.026-1.205) | | |
| Sex | | | | | | | | |
| Male *vs*. Female (Ref) | 0.520 | 1.484 (0.446-4.938) | | | 0.871 | 1.133 (0.252-5.082) | | |
| Positive preoperative urine cytology | | | | | | | | |
| Yes | 0.008 | 3.233 (1.356-7.705) | 0.285 | 1.773 (0.621-5.061) | 0.018 | 6.210 (1.373-28.088) | 0.328 | 2.584 (0.386-17.286) |
| History of BCG instillation | | | | | | | | |
| Yes | <0.001 | 4.469 (2.062-9.687) | 0.002 | 4.439 (1.725-11.422) | <0.001 | 8.032 (2.774-23.255) | 0.005 | 8.534 (1.898-38.370) |
| Recurrence case | | | | | | | | |
| Yes | 0.149 | 1.760 (0.816-3.794) | | | 0.073 | 2.890 (0.906-9.223) | | |
| Tumor size† | 0.696 | 1.093 (0.700-1.705) | | | 0.352 | 1.286 (0.757-2.185) | | |
| Multiplicity | | | | | | | | |
| Multiple *vs*. Single (Ref) | 0.012 | 2.903 (1.268-6.646) | 0.154 | 2.459 (0.713-8.479) | 0.066 | 2.967 (0.929-9.476) | 0.599 | 1.677 (0.244-11.522) |
| Pathological T-stage | | | | | | | | |
| T1 *vs*. Ta (Ref) | 0.036 | 2.433 (1.060-5.582) | 0.376 | 1.655 (0.542-5.050) | 0.003 | 6.087 (1.824-20.316) | 0.113 | 5.072 (0.682-37.731) |
| Tumor grade | | | | | | | | |
| High *vs*. Low (Ref) | 0.106 | 2.728 (0.808-9.209) | | | 0.644 | 1.451 (0.299-7.032) | | |
| Concurrent CIS | | | | | | | | |
| Yes | 0.166 | 1.767 (0.789-3.957) | | | 0.213 | 2.016 (0.669-6.073) | | |
| Complete resection | | | | | | | | |
| Yes | 0.109 | 0.412 (0.140-1.218) | 0.120 | 0.327 (0.080-1.338) | 0.053 | 0.269 (0.071-1.015) | 0.141 | 0.255 (0.041-1.572) |
| EAU risk classification | | | | | | | | |
| High/Very high *vs*. Low/Intermediate (Ref) | 0.018 | 2.862 (1.199-6.831) | 0.356 | 1.814 (0.512-6.427) | 0.086 | 3.149 (0.849-11.680) | 0.656 | 1.735 (0.154-19.595) |
| Adjuvant instillation | | | | | | | | |
| Yes | 0.596 | 0.809 (0.369-1.772) | | | 0.394 | 1.744 (0.485-6.269) | | |

†Continuous variable. HR: Hazard ratio; CI: confidence interval; Ref: reference; BCG: Bacillus Calmette-Guérin; CIS: carcinoma in situ; EAU: European Association of Urology.

$p$=0.005) (Table IV). The 1-year cumulative recurrence rates were 66.2% and 16.5%, respectively ($p$<0.001; Figure 3A), and progression rates were 50.4% and 3.5%, respectively ($p$<0.001; Figure 3B), for patients with and without prior BCG intravesical instillation.

*Treatment-related toxicities*. Of the 105 patients, 9 (8.6%) experienced liver dysfunction, of which 5 were grade 1, 3 were grade 2, and 1 was grade 3. About 15 patients (14.3%) experienced nausea with grade 1; 18 patients (17.1%) experienced hypotension, of which 5 were grade 1 and 13 were grade 2; and 2 patients (1.9%) experienced hypoxia with grade 1. No severe, life-threatening adverse reactions were observed.

## Discussion

PDD-assisted TURBT using ALA is becoming increasingly popular in Japan, and its usefulness has been reported in several studies (3, 4, 6, 7). Moreover, several recent systematic reviews revealed that TURBT with PDD could reduce BC recurrence and resulted in a progression risk reduction compared to conventional TURBT with WL (13-15). This retrospective study found that FL had significantly higher sensitivity and lower specificity than WL, similar to previous reports (5, 16). PDD sensitivity was more than 50% higher than that of WL in diagnostic accuracy for CIS, reflecting ALA-PDD strength. Although a recent meta-analysis reporting 1-year recurrence-free survival with ALA-PDD was 50.4-89.6% (*vs*. 39.0-85.0% for WL) (14), the 1-year recurrence rate in the present study was similar.

This present study interestingly showed that a BCG instillation history was independently associated with intravesical recurrence and disease progression. Intravesical BCG immunotherapy can prevent recurrence (17-19) and potentially lower the risk of tumor progression (20, 21). Actually, of the 17 patients with an intravesical BCG infusion history, 11 and 8 patients experienced recurrence and progression, respectively. In particular, 7 patients were diagnosed with BCG unresponsive disease; 6 patients developed recurrence, and 5 patients developed MIBC or metastatic disease, supporting their poor prognosis. Thus, frequent cystoscopy and imaging tests may be necessary for postoperative patient follow-up with a BCG administration history or BCG unresponsive disease.

ALA's main adverse effects reported to date include liver dysfunction, photosensitivity, hypotension, and gastrointestinal symptoms such as nausea, vomiting, and abdominal pain (5, 22, 23). The present study showed that there were fewer elevated liver enzymes, more nausea, and no severe hypotension of grade 3 or higher was observed, although a randomized controlled trial reported that the incidences of elevated liver enzymes, gastrointestinal symptoms, and severe hypotension were 18.0-24.6%, 8.1%, and 1.6%, respectively (5). Therefore, PDD-assisted TURBT using ALA can be safely performed.

This study has some limitations, such as its retrospective design, small patient number, and insufficient follow-up period to draw a firm conclusion. A comparison with conventional TURBT is additionally necessary in order to discuss ALA's therapeutic effects. Moreover, various adjuvant instillation therapy may have enhanced the therapeutic effect after PDD assisted TURBT. Therefore, we hope to continue examining this issue in the future with additional patients and a longer observation period.

In conclusion, the present study showed that PDD-assisted TURBT using ALA contributed to a higher sensitivity in detecting tumors, particularly for CIS, compared to WL. Additionally, BCG instillation history, particularly BCG unresponsive disease, was a poor cancer recurrence and progression prognostic factor for NMIBC patients undergoing PDD-assisted TURBT, and special attention should be paid to postoperative follow-up.

## Conflicts of Interest

The Authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Authors' Contributions

All Authors participated in this article's writing and revision. T Makino has full access to all data in the study, and takes responsibility for data integrity and data analysis accuracy. Study concept and design: T Makino and M Ofude. Acquisition, analysis, or interpretation of data: T Makino. Drafting of the manuscript: T Makino. Critical manuscript revision for important intellectual content: T Kawahara, T Hori, and S Urata. Study supervision: T Miyagi. All Authors read and approved the final manuscript.

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