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ORIGINAL ARTICLE

# Comparative assessment of disease recurrence after transurethral resection of non-muscle-invasive bladder cancer with and without a photodynamic diagnosis using 5-aminolevulinic acid: a propensity score-matching analysis

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## Abstract

**Background** Among patients with non-muscle-invasive bladder cancer (NMIBC), systematic reviews showed lower recurrence rate in patients treated with photodynamic diagnosis (PDD)-assisted transurethral resection of bladder tumor (TURBT) than with white-light (WL) TURBT. However, the result is not consistent between clinical trials and the significance of preoperatively available factors in disease recurrence after PDD-TURBT remains unclear.

**Methods** The present study retrospectively analyzed 1174 NMIBC patients who underwent TURBT and were followed up for ≥ 6 months. Among 1174 patients, 385 and 789 underwent PDD-TURBT with oral 5-aminolevulinic acid (the PDD group) and WL-TURBT (the WL group), respectively. Recurrence-free survival (RFS) was compared between the PDD and WL groups before and after propensity score matching, and the impact of several baseline parameters on RFS between the 2 groups was investigated after matching.

**Results** Before propensity score matching, RFS was significantly longer in the PDD group than in the WL group ($P = 0.006$). After matching, 383 patients were included in both groups, and RFS was significantly longer in the PDD group than in the WL group ($P < 0.001$). In the cohort after matching, RFS between the two groups was compared in each subgroup classified according to baseline parameters, including age, sex, history of previous or concomitant upper urinary tract urothelial carcinoma, preoperative urinary cytology, tumor multiplicity, and tumor size, and significantly longer RFS was observed in the PDD group in all subgroups, except for the patients with tumors ≥ 30 mm ($P = 0.21$).

**Conclusion** These results suggest that PDD-TURBT prolongs RFS in NMIBC patients, except for those with tumors ≥ 30 mm.

**Keywords** PDD-TURBT · RFS · Propensity score matching · Tumor size

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## Introduction

Bladder cancer is the seventh and 17th most commonly diagnosed cancer in males and females, respectively, with age-standardized incidence rates of 9.5 and 2.4 per 100,000 person/year, respectively [1]. Approximately 75% of patients with bladder cancer are diagnosed with non-muscle-invasive bladder cancer (NMIBC) [1]. Due to the high risks of disease recurrence and progression after transurethral resection of bladder tumor (TURBT) under simple white-light (WL) guidance in NMIBC patients, additional management strategies, including intravesical instillation therapy, second TUR, and photodynamic diagnosis (PDD) under blue-light guidance, have been developed to improve the prognostic outcomes of these patients, and these advantages have been widely recognized in recent years.

Several systematic reviews and meta-analyses demonstrated that PDD-TURBT using 5-aminolaevulinic acid (5-ALA) or hexaminolevulinic acid increased detection rate of tumors, particularly that of CIS [2] and reduced the risk of disease recurrence more than WL-TURBT in patients with NMIBC [3, 4]. Furthermore, progression to muscle invasive disease was effectively inhibited by PDD-TURBT [4]. However, the oncological benefits of PDD-TURBT reported in several randomized control studies differed [5–8]. In addition, PDD is known to be accompanied by several adverse events, such as photosensitivity, liver injury, and hypotension [9, 10], and the cost-effectiveness of PDD-TURBT remains controversial [8, 11, 12]. Accordingly, PDD-TURBT is not strongly recommended or is only recommended for limited cohorts in major clinical guidelines [13, 14].

Based on these findings, it is important to preoperatively identify patients expected to benefit from PDD-TURBT. Although previous studies identified factors associated with oncological outcomes in NMIBC patients receiving PDD-TURBT, most included an insufficient number of patients and/or conducted assessments based on factors unavailable prior to surgery. Therefore, the present study included 1174 patients with NMIBC who were treated with PDD-TURBT or WL-TURBT and subsequently observed for ≥ 6 months, and the significance of baseline parameters before TURBT was evaluated as predictors of recurrence-free survival (RFS) according to the type of TURBT.

## Patients and methods

### Patients

This retrospective multicenter study was approved by each Ethics Committee of the participating institutions (No. 21-058). Informed consent was obtained from the participants or deceased patients' families through posters and/or websites using the opt-out method.

After the exclusion of patients with an observation period < 6 months following TURBT and/or missing data for analyses, the present study examined 1174 consecutive patients with primary NMIBC, consisting of 385 and 789 who underwent PDD-TURBT with oral 5-ALA under blue-light guidance (the PDD group) and non-PDD-TURBT under WL guidance (the WL group), respectively, between February 2006 and June 2021 at Nara Medical University Hospital, Saitama Medical University International Medical Center, Hamamatsu University Hospital, Kochi Medical School Hospital, and Yamaguchi University Hospital. The following clinicopathological data of the patients included were obtained from their medical records at each hospital: age, sex, previous or concomitant history of upper urinary tract urothelial cancer (UTUC), preoperative cytology, tumor multiplicity, tumor size, pathological T stage, concomitant carcinoma in situ (CIS), second TURBT, intravesical bacillus Calmette–Guérin (BCG) therapy, including both induction and maintenance therapies, and intravesical chemotherapy, including both single immediate and adjuvant instillation therapies, adverse events, and follow-up data.

### Surgical procedure, postoperative therapy, and follow-up protocol

In the PDD group, approximately 3 h (range, 2–4 h) before surgery, patients orally received 5-ALA hydrochloride (SBI Pharmaceuticals Co., Ltd., Tokyo, Japan) in water at a dose of 20 mg/kg. The procedures and instruments used for anesthesia and the two types of TURBT were described in detail in our previous studies [15–17]. Each physician decided whether the following postoperative management approach was performed: the intravesical adjuvant administration of anthracyclines, the intravesical administration of BCG, and second TUR. Patients were followed-up with routine cystoscopy combined with urine cytology and imaging examinations at regular intervals according to contemporary clinical practice guidelines.

### Statistical analysis

Statistical analyses were performed using SPSS software Version 28.0 (IBM Corp., Chicago, IL, USA). Clinical characteristics between the PDD and WL groups were compared using the chi-square test for categorical variables. To evaluate the efficacy of PDD-TURBT, RFS was calculated as the length of time from initial TURBT to pathologically diagnosed intravesical recurrence or overall death by the Kaplan–Meier method, and differences in RFS between the PDD and WL groups were compared using the Log-rank

**Table 1** Characteristics of patients in the whole cohort

| Variables | PDD group N = 385 | WL group N = 789 | *P* |
|---|---|---|---|
| Age (years) | | | 0.58 |
| < 70 | 141 | 276 | |
| ≥ 70 | 244 | 513 | |
| Sex | | | 0.078 |
| Male | 331 | 646 | |
| Female | 54 | 143 | |
| UTUC history | | | 0.63 |
| No | 366 | 755 | |
| Yes | 19 | 34 | |
| Cytology | | | 0.95 |
| Negative | 135 | 278 | |
| Equivocal or positive | 250 | 511 | |
| Tumor multiplicity | | | 0.38 |
| Solitary | 172 | 374 | |
| Multiple | 213 | 415 | |
| Tumor size | | | 0.82 |
| < 30 mm | 319 | 658 | |
| ≥ 30 mm | 66 | 131 | |
| pT category | | | 0.85 |
| Ta | 222 | 455 | |
| T1 | 139 | 291 | |
| Isolated Tis | 24 | 43 | |
| Concomitant CIS | | | 0.58 |
| No | 296 | 618 | |
| Yes | 89 | 171 | |
| Second TUR | | | 0.004 |
| No | 285 | 641 | |
| Yes | 100 | 148 | |
| BCG therapy | | | 0.10 |
| No | 248 | 546 | |
| Yes | 137 | 243 | |
| Intravesical chemotherapy | | | 0.081 |
| No | 286 | 622 | |
| Yes | 99 | 167 | |

test. A propensity score matching analysis was performed using a 1:1 and 1.2 nearest neighbor matching algorithm without replacement with distances assessed by logistic regression. The analysis was performed based on age, sex, previous or concomitant history of UTUC, preoperative cytology, tumor multiplicity, tumor size, pathological T stage, concomitant CIS, second TURBT, and intravesical BCG therapy, including both induction and maintenance therapies. Covariate distributions between patients undergoing PDD-TURBT or WL-TURBT were balanced after conditioning on the propensity score, with a difference of < 0.1 in the standardized difference after matching being considered to indicate a good balance. After propensity score

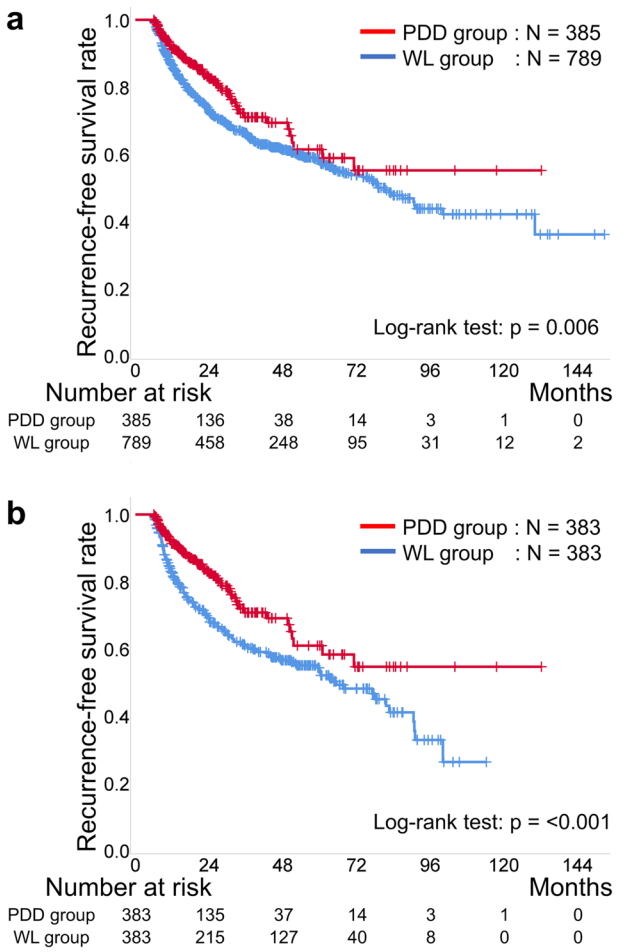


**Fig. 1** Kaplan–Meier curves of recurrence-free survival (RFS) and the *P* value calculated by the Log-rank test between PDD and WL groups. **a** A comparison of 1174 patients in the entire cohort before propensity score matching. **b** A comparison of 776 patients after propensity score matching population

matching, each preoperative baseline factor that contributed to longer RFS in the PDD group than in the WL group was analyzed in subgroups using Cox's proportional hazards regression model. $P < 0.05$ (two-sided) were considered to be significant.

## Results

Among the 1174 patients included in the present study, 385 and 789 were classified into the PDD and WL groups, respectively. The clinicopathological characteristics of these patients are shown in Table 1. Although significant differences were only observed in the percentage of patients undergoing second TUR between the PDD and WL groups, the unbalanced distribution of some factors was noted between the two groups.

Median observation periods were 19.9 and 29.7 months in the PDD and WL groups, respectively. During the observation period, disease recurrence or overall death occurred in 71 (18.4%) and 293 (37.1%) patients in the PDD and WL groups, respectively. Median RFS was not reached and was 79.0 months in the PDD and WL groups, respectively, and was significantly longer in the former than in the latter ($P = 0.006$) (Fig. 1a).

To adjust for imbalances in baseline characteristics, including age, sex, previous or concomitant history of UTUC, preoperative cytology, tumor multiplicity, tumor size, pathological T stage, concomitant CIS, second TURBT, and intravesical BCG therapy, between the two groups, 1:1 propensity score matching was performed. Following propensity score matching, 383 patients were included in both groups, and backgrounds between the two groups were statistically balanced (Table 2).

In the propensity score matching cohort, RFS was not reached and was 65.5 months in the PDD and WL groups, respectively. As shown in Fig. 1b, RFS was significantly longer in the PDD group than in the WL group ($P < 0.001$). Subgroup analyses of RFS were presented as forest plots in Fig. 2. In the subgroup with tumors ≥ 30 mm, no significant difference was noted in RFS between the two groups (HR 0.68, 95% CI 0.38 to 1.23, $P = 0.21$); however, in the remaining subgroups, RFS was significantly longer in the PDD group than in the WL group. Figure 3 shows Kaplan–Meier curves according to tumor sizes after propensity score matching. Among patients with tumors < 30 mm, RFS was significantly longer in the PDD group than in the WL group ($P < 0.001$), but was not in those with tumors ≥ 30 mm ($P = 0.20$). In addition, according to European Association of Urology (EAU) NMIBC risk group based on 2021 EAU NMIBC scoring model, PDD group had significantly longer

**Table 2** Characteristics of the propensity score matching population

| Variables | PDD group N = 383 | WL group N = 383 | *P* | Standardized difference |
|---|---|---|---|---|
| Age (years) | | | 0.82 | 0.016 |
| < 70 | 141 | 138 | | |
| ≥ 70 | 242 | 245 | | |
| Sex | | | 0.84 | 0.015 |
| Male | 329 | 327 | | |
| Female | 54 | 56 | | |
| UTUC history | | | 0.87 | 0.012 |
| No | 364 | 363 | | |
| Yes | 19 | 20 | | |
| Cytology | | | 0.26 | 0.081 |
| Negative | 134 | 149 | | |
| Equivocal or positive | 249 | 234 | | |
| Tumor multiplicity | | | 0.56 | 0.042 |
| Solitary | 172 | 164 | | |
| Multiple | 211 | 219 | | |
| Tumor size | | | 0.92 | 0.006 |
| < 30 mm | 318 | 319 | | |
| ≥ 30 mm | 65 | 64 | | |
| pT category | | | 0.66 | 0.032 |
| Ta | 221 | 215 | | |
| T1 or isolated Tis | 162 | 168 | | |
| Concomitant CIS | | | 0.55 | 0.043 |
| No | 295 | 288 | | |
| Yes | 88 | 95 | | |
| Second TUR | | | 0.33 | 0.070 |
| No | 285 | 273 | | |
| Yes | 98 | 110 | | |
| BCG | | | 0.94 | 0.005 |
| No | 248 | 247 | | |
| Yes | 135 | 136 | | |

RFS than WL group in the high-risk group, but not in the remaining 3 groups (Fig. 4).

As common adverse events associated with PDD, the incidences of liver injury and hypotension were investigated as follows: liver injury occurred in 5.5% (n = 21) and 0.6% (n = 5) in the PDD group and WL groups, respectively ($P < 0.001$), and hypotension in 4 patients (1.0%) and 2 patient (0.5%), respectively (P = 0.69). In addition, one patient (0.3%) in PDD group developed photosensitivity.

## Discussion

The combination of PDD with TURBT is generally regarded as a beneficial approach for patients with NMIBC. Veeratterapillay et al. recently conducted a systematic review and meta-analysis including randomized control trials that evaluated the postoperative outcomes of WL- and PDD-TURBT, and found that PDD-TURBT increased recurrence-free rate at both 12 and 24 months [3], while an abridged Cochrane review showed that PDD-TURBT reduced the risk of both disease recurrence and progression more than WL-TURBT [4]. However, several issues associated with the combination of PDD and TURBT have been reported, such as inconsistent prognostic benefits in prospective studies [5–8, 18–21] and false-positive findings [2]; therefore, PDD-TURBT is recommended under limited conditions in major guidelines [13, 14]. Based on these findings, we conducted a retrospective multi-center study that included 1174 NMIBC patients who underwent TURBT and were followed up for ≥ 6 months in order to assess the prognostic impact of PDD-TURBT and identify the cohort most likely to benefit from PDD-TURBT.

A previous systematic review reported that 2-year RFS rates were between 40.0 and 89.6% and between 28.0 and 72.0% in the PDD and WL groups, respectively [3]. In the entire cohort of this study before propensity score matching, 2-year RFS rates were 82.5 and 73.2% in the PDD and WL groups, respectively, suggesting similar or even superior postoperative disease control to those in previous studies. In this series, RFS was significantly longer in the PDD group than in the WL group before matching. Furthermore, after matching, which balanced all of the parameters examined, RFS was also significantly longer in the PDD group than in the WL group. Therefore, the present results suggest that PDD-TURBT significantly prolonged RFS because the effects of imbalanced baseline parameters on RFS were markedly reduced by propensity score matching from those in a simple observational study.

| | | Number of event / n | | | |
|---|---|---|---|---|---|
| | | WL group N=383 | PDD group N=383 | HR | p |
| PSM cohort | | 163/383 | 71/383 | 0.59 (0.44 – 0.78) | < 0.001 |
| Age | <70 | 61/138 | 28/141 | 0.59 (0.38 – 0.93) | 0.023 |
| | ≥70 | 102/245 | 43/242 | 0.59 (0.41 – 0.84) | 0.004 |
| Sex | Male | 136/327 | 62/329 | 0.63 (0.47 – 0.86) | 0.003 |
| | Female | 27/56 | 9/54 | 0.40 (0.19 – 0.85) | 0.018 |
| UTUC history | No | 148/363 | 67/364 | 0.62 (0.46 – 0.84) | 0.002 |
| | Yes | 15/20 | 4/19 | 0.26 (0.086 – 0.76) | 0.017 |
| Cytology | Negative | 69/149 | 22/134 | 0.48 (0.30 – 0.79) | 0.004 |
| | Equivocal or positive | 94/234 | 49/249 | 0.66 (0.46 – 0.94) | 0.020 |
| Tumor multiplicity | Solitary | 61/164 | 25/172 | 0.61 (0.38 – 0.98) | 0.039 |
| | Multiple | 102/219 | 49/211 | 0.58 (0.41 – 0.82) | 0.002 |
| Tumor size | < 30 mm | 131/319 | 53/318 | 0.56 (0.41 – 0.78) | < 0.001 |
| | ≥ 30 mm | 32/64 | 18/65 | 0.68 (0.38 – 1.23) | 0.21 |

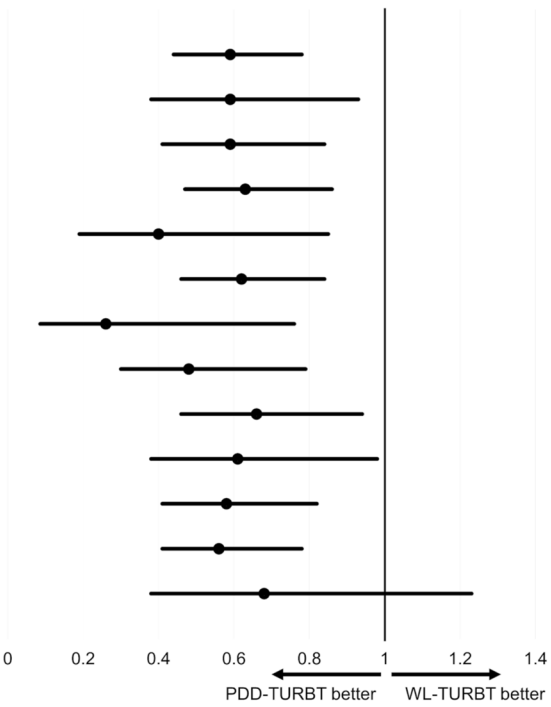


**Fig. 2** Recurrence-free survival (RFS) according to subgroups of preoperatively evaluable factors. The number of events/the number of patients and forest plots according to subgroups. The hazard ratio (HR) (median, range) and *P* value were analyzed by Cox's proportional hazard analysis

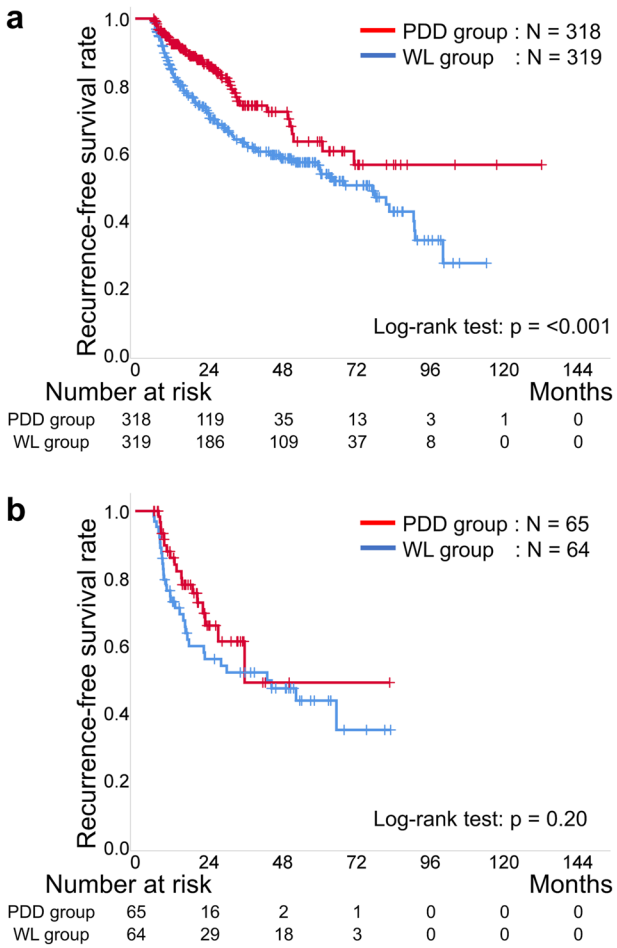


**Fig. 3** Kaplan–Meier curves of RFS and the *P* value calculated by the Log-rank test between PDD and WL groups in the propensity score matching population. **a** Patients with tumors < 30 mm. **b** Patients with tumors ≥ 30 mm

A number of disadvantages of PDD-TURBT have been reported [2, 9, 10, 22, 23]. For example, the oral administration of 5-ALA rarely induced severe hypotension and liver toxicity [9, 10]. In fact, the incidence of liver injury was significantly higher in the PDD group and one patient developed photosensitivity after administration of 5-ALA in this series. Furthermore, regarding the oral administration of 5-ALA, patients need to be tolerant of an acidic taste, avoid phototoxic drugs, and reduce their exposure to sunlight or room light in order to prevent photosensitivity [24]. Accordingly, it is important to preoperatively select optimal candidates who will achieve prognostic benefits by PDD in combination with TURBT; however, few studies have investigating these issues [21, 25]. The present assessment of subgroups classified according to several preoperatively evaluable factors after propensity score matching revealed that PDD-TURBT was effective for the majority of NMIBC patients, except for those with tumors ≥ 30 mm. Kobayashi et al. reported similar findings to the results of our subgroup analyses; recurrence within < 500 days after PDD-TURBT was not significantly reduced in NMIBC patients with tumors ≥ 30 mm [25]. Although it was characterized in detail, the lack of prognostic benefits in patients with tumors ≥ 30 mm after PDD-TURBT may be associated with a long operative time during the management of large tumors because the stability of protoporphyrin IX induced by 5-ALA is known to be dependent on the wavelength and intensity of light used during surgery, while its elimination (photobleaching) is accelerated during WL cystoscopy [2].

There are several limitations that need to be addressed. Initially, adjuvant therapy and the follow-up protocol were not standardized, because data were retrospectively acquired from multiple institutions for a long period. In particular, detailed information, regarding intravesical instillation therapy with BCG and chemotherapeutic agent was not available. Secondly, sample in each subgroup was comparatively small to conclude the effectiveness of PDD-TURBT, especially, in patients with tumors ≥ 30 mm. Furthermore, the prognosis of patients may have been affected by differences in the skill of surgeons; however, multiple surgeons, even in each institution, were involved. Moreover, due to the study period between 2006 and 2020, tumor grades were excluded from statistical analyses and the cytology-reporting system was not standardized as The Paris System. Thirdly, variables for propensity score matching were not selected based on subjective criteria in this study. For example, it may be controversial to include CIS as a variable of propensity score matching, since detection of CIS is one of the advantages of PDD-TURBT. However, a systematic-review and meta-analysis indicated the incidence of CIS was not always high in PDD group [3], and concomitant CIS is a well-recognized major factor influencing RFS. Accordingly, to balance the background involving risk of recurrence, we included CIS as the variables of matching, like a previous report [25]. Lastly, the retrospective design of this study may lead to limited ability to accurately capture AEs; thus, it should be considered that adverse events could be under-reported.

In conclusion, RFS was significantly longer in the PDD group than in the WL group in both the entire cohort and propensity score matching cohort. However, subgroup analyses showed no significant differences in RFS between patients with tumors ≥ 30 mm who underwent PDD-TURBT or WL-TURBT.

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**Author contributions** All authors contributed to the study conception and design. Data collection and analyses were performed by YM, MM,

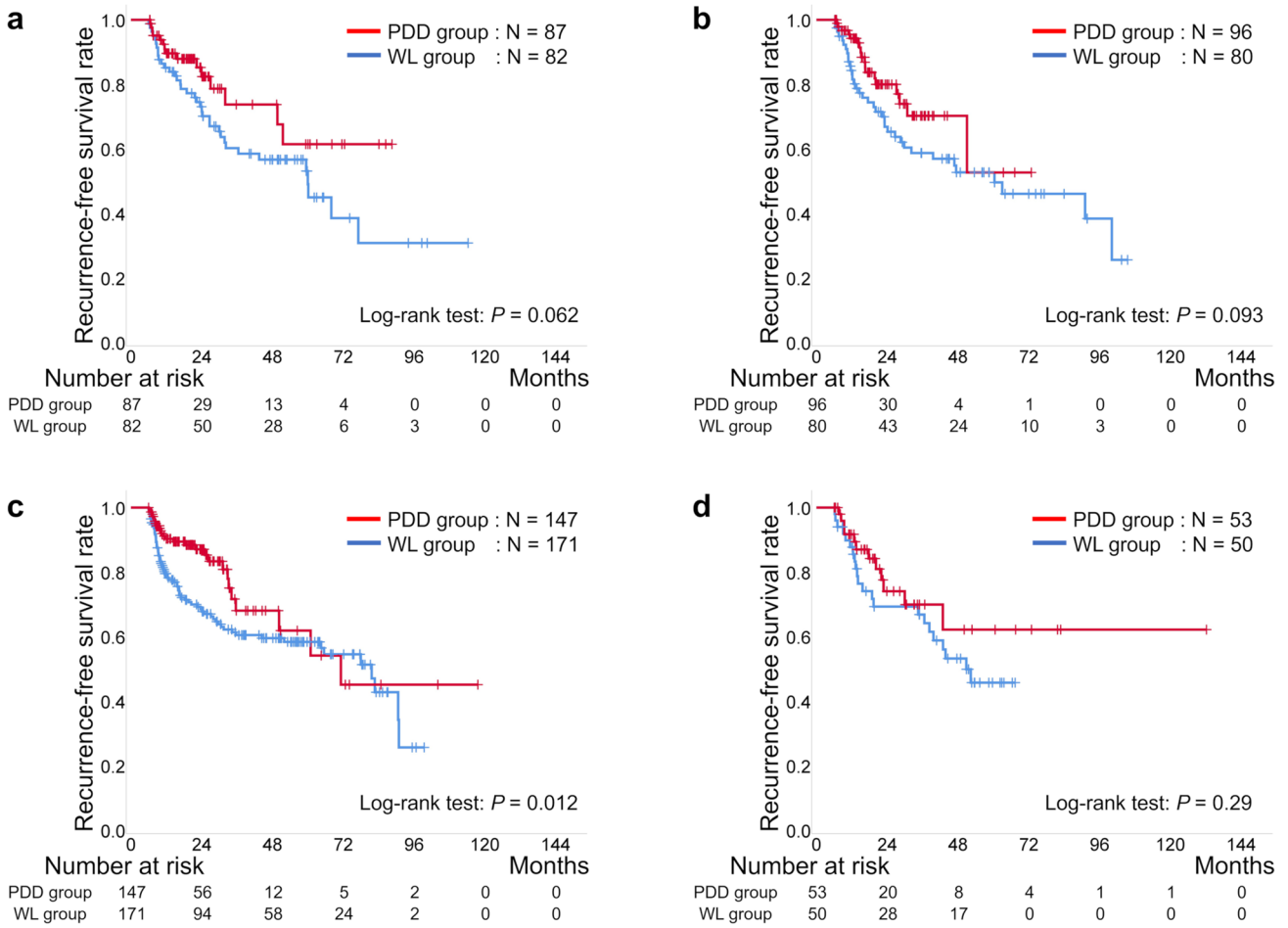


**Fig. 4** Kaplan–Meier curves of RFS and the *P* value calculated by the Log-rank test between PDD and WL groups in the propensity score matching population according to EAU risk group. **a** Low risk. **b** Intermediate risk. **c** High risk. **d** Very high risk

KN, HF, and KK. The first draft of the manuscript was written by YM and HM and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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## Declarations

**Conflict of interest** Hideyasu Matsuyama received lecture fees from Nippon Kayaku Co.,Ltd; the other authors declare that they have no conflict of interest.

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