DaBlaCa-11: Photodynamic Diagnosis in Flexible Cystoscopy—A Randomized Study With Focus on Recurrence

Ditte Drejer, Anne-Louise Moltke, Anna Munk Nielsen, Gitte W. Lam, and Jørgen Bjerggaard Jensen

OBJECTIVE To examine whether photodynamic diagnosis (PDD) in addition to *flexible* cystoscopy in the outpatient clinic can reduce risk of tumor recurrence in patients with previous nonmuscle invasive bladder cancer. PDD is an optical technique that enhances the visibility of pathologic tissue and helps guidance tumor resection.

METHODS From February 2016 to December 2017, 699 patients from 3 urologic departments in Denmark were enrolled in a randomized controlled trial. Four months after transurethral resection of bladder tumor patients were randomized 1:1 to either an intervention group (hexaminolevulinate was instilled in the bladder before flexible cystoscopy with PDD video cystoscope) or a control group (white light flexible cystoscope), only. Primary endpoint was tumor recurrence within 8 months from the randomization. Secondary outcomes were numbers of procedures in general anesthesia, time to the first recurrence, differences in tumor size, risk of tumor progression, and identification of carcinoma in situ.

RESULTS A total of 351 patients were allocated to the intervention group (flexible PDD), and 348 to the control group (flexible white light). Throughout the following 8 months after randomization, only 117 patients in the intervention group had at least 1 tumor recurrence compared to 143 patients in the control group (P = .049). Odds ratio of 0.67 (P = .02, 95% CI: 0.48-0.95) correlates with a tumor reduction of 33% in favor of the intervention group.

CONCLUSION Use of PDD in a routine surveillance cystoscopy first time after transurethral resection of bladder tumor for nonmuscle invasive bladder cancer reduces subsequent risk of tumor recurrence compared to WL cystoscopy alone. UROLOGY 137: 91–96, 2020. © 2019 Elsevier Inc.

Bladder cancer is the 11th most common cancer worldwide when both genders are considered.[1] Every year, approximately 1500 men and 550 women are diagnosed in Denmark.[2] Three out of four new cases of bladder cancer patients present with a nonmuscle invasive bladder cancer (NMIBC) confined to the mucosa (stage Ta or carcinoma in situ) or submucosa (stage T1).[1] In many patients, the disease affects all of the urothelium, and therefore multiple recurrent tumors can occur after the primary transurethral resection of the bladder (TURBT).[3] Tumor recurrence will usually require another TURBT under general anesthesia that can cause postoperative irritation of both bladder and urethra. Thus, there is a high incidence of pollakisuria, nocturia causing sleep disturbance, urge and dysuria, following the TURBT.[4,5] For some patients, this can continue for months. However, if a tumor recurrence is detected at a very early stage, and thereby small size, it is possible to treat more patients in an outpatient setting at their routine surveillance cystoscopy and thereby reduce the numbers of TURBT's, the associated cost, and discomfort of the patients.[6]

Photodynamic diagnosis (PDD) is an optical technique that enhances the visibility of pathologic tumor tissue and thereby helps guidance tumor resection during TURBT. This is caused by an interaction between a photosensitive instillation of Hexaminolevulinate (HAL) that accumulates in tissue with pathology due to altered enzymes activity combined with illumination with blue light (380-440 nm).

Running description head: Our objective was to examine whether PDD in addition to flexible cystoscopy in the outpatient clinic can reduce risk tumor of tumor recurrence in patients with previous nonmuscle invasive bladder cancer (NMIBC). We found PDD-flexible cystoscopies reduced the risk of tumor recurrences with 33% within 8 months.

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From the Department of Urology, Regional Hospital of West Jutland, Holstebro, Denmark; the Department of Clinical Medicine, Health, Aarhus University, Aarhus, Denmark; the Department of Urology, Aarhus University Hospital, Aarhus, Denmark; and the Department of Urology, Herlev and Gentofte, Denmark

Address correspondence to: Ditte Drejer, Ph.D., M.D., Department of Urology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus, Denmark. E-mail: Dittedrejer@dadlnet.dk

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This will make any pathologic or abnormal tissue emit red fluorescence and thereby creating a contrast between normal and pathologic tissue.[7] In the literature, there are several studies and reviews published on HAL PDD-guided tumor detection compared with standard white light (WL). A higher detection rate, longer recurrence-free interval, and a more complete tumor resection are the main advantages of PDD.[7-11] However, most studies on PDD are based on rigid cystoscopy and TURBT whereas few feasibility studies, and only 1 randomized study of detection rate, are published on PDD flexible cystoscopy.[6,12-15]

This study is the first randomized clinical trial performed in a large multicentre setting examining whether PDD-guided flexible cystoscopy at the time of first follow-up after TURBT can reduce the risk of later tumor recurrences compared to conventional WL cystoscopy.

MATERIALS AND METHOD

From February 2016 to December 2017, we enrolled 699 consecutive patients from 3 urologic departments in Denmark in this randomized controlled trial. Patients were included at the time of first follow-up cystoscopy 4 months after TURBT because of noninvasive Ta-tumor. Patients with both previous high-grade and low-grade tumors were included. All patients were above 18 years of age, able to understand and speak Danish, and able to sign the consent form. Exclusion criteria were symptomatic urinary tract infection at the time of cystoscopy, pregnancy or breastfeeding, long-term indwelling catheters, known allergy to HAL, and adjuvant Bacillus Calmette-Guérin (BCG), or Mitomycin C treatment after the latest TURBT. Single shot Mitomycin C at the time of TURBT was accepted. An online randomization tool allocated patients 1:1 of unknown block sizes, to either standard WL flexible cystoscopy (control group), or PDD-guided flexible cystoscopy after 50 mL of HAL (Hexvix, Photocure ASA, Norway) was instilled in the bladder for at least 1 hour (intervention group). The same urologist performed all cystoscopies using PDD Videocystoscope 11272 VPI, D-Light C-Light Source and Telecam (KARL STORZ, Germany). Bendable forceps (single-use biopsy forceps 110274-01, work length 1200 mm and diameter 5 Fr, MTP, KARL STORZ, Germany), and electrofulguration were available at all study sites. Outpatient biopsy of suspicious mucosa and treatment of 3-4 tumors of 0.5-1 cm was feasible. The 3 recruitment centers did not have the same access to perform biopsies. Additionally, none of the centers had the equipment available to perform PDD flexible cystoscopy outside of the trial. Any recurrences not suitable for outpatient treatment would be scheduled for a TURBT within 1-2 weeks. After study enrolment, patients continued their surveillance program according to the Danish Guidelines on NMIBC. In this, patients with high-grade tumors undergo flexible WL cystoscopy every 4 months for 2 years followed by lifelong annual cystoscopy if recurrence free. This is often combined with BCG instillation therapy for the first year if multiple or recurrent tumors are diagnosed. Patients in low- and intermediate-risk groups will undergo flexible WL cystoscopy 4 months after TURBT, then 8 months later, and then annually thereafter if no recurrences are found.[16]

Primary endpoint of this study was tumor recurrence rate in an 8-month period after study enrolment, thus, recurrence within the first year after the latest TURBT, but not including findings at the cystoscopy at the time of randomization. Secondary outcomes were numbers of procedures (TURBT's) in general anesthesia within 12 months from the latest TURBT, time to the first recurrence, size of tumor recurrences, risk of tumor progression, and identification of carcinoma in situ.

A sample size calculation tool was used and performed from an assumption of an overall 35% risk of recurrence within 12 months from latest TURBT. We expected the overall risk of having a tumor recurrence at 4 months cystoscopy to be 15% and additional 20% in risk of having recurrences in the subsequent 8 months of follow-up. Difference between the 2 groups were based on an assumption of reduction of one-third (7% absolute risk reduction) within 8 months after randomization in favor of using PDD at 4-month follow-up cystoscopy. A power at 80% and a significant level at 5% were chosen. Thus, each study arm should include 348 patients and 696 patients in total.

Descriptive statistics compared the results within the 2 groups using Pearson's chi-squared test with a 2-sided significance level of 5%. Analysis of tumor recurrences was evaluated using a logistic regression model. Mann-Whitney *U* test was used for the calculation of differences in numbers of TURBT's. Time to first recurrence was analyzed by the Kaplan-Meier method.

Ethical approval was obtained from the Danish Medicines Agency (EudraCT 2015 000 346-15), the Danish Data Protection Agency (no: 207-58-0010), and the Regional Committee on Health Research Ethics (M 2015 76.15). The study was registered in ClinicalTrials.gov (NCT02660190).

RESULTS

A total of 351 patients were allocated to the intervention group (flexible PDD), and 348 to the control group (flexible WL). Demographic data are shown in Table 1. Four patients (*n*: 2 intervention, *n*: 2 control) did not get a cystoscopy at the time of enrolment because of urethral stricture, phimosis, or unrecognized cystitis making the cystoscopy impossible or not relevant at the current visit (Fig. 1). At the time of randomization, there was no significant difference between tumor detection rate when

Table 1. Patient characteristics, *n*: 699

Treatment arm	Control	Intervention	*P* Value
Number (%)	348 (49.8)	351 (50.2)	.99
Gender			
Male (%)	247 (35.3)	252 (36.1)	.81
Female (%)	101 (14.4)	99 (14.1)	.81
Age (y), mean (range)	69.9 (22-97)	70.3 (22-97)	.47
Previous CIS (%)	17 (2.4)	18 (2.6)	.88
Previous BCG treatment (%)	30 (4.3)	34 (4.9)	.63
Single-shot MMC* latest TURBT (%)	93 (13.3)	105 (15.0)	.35
PDD used at latest TURBT (%)	256 (36.6)	272 (38.9)	.23
Histopathology of the †*initial* TURBT at the time of the diagnosis (%)			
Ta LG	263 (33.8)	275 (39.3)	
Ta HG	75 (10.7)	63 (9.01)	
T1a	10 (1.4)	13 (1.9)	.43

BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; MMC, Mitomycin C; PDD, photodynamic diagnosis; TURBT, transurethral resection of bladder tumor.
* Latest TURBT: TURBT 4 months previous.
† Initial TURBT: First TURBT with diagnosis of NMIBC.

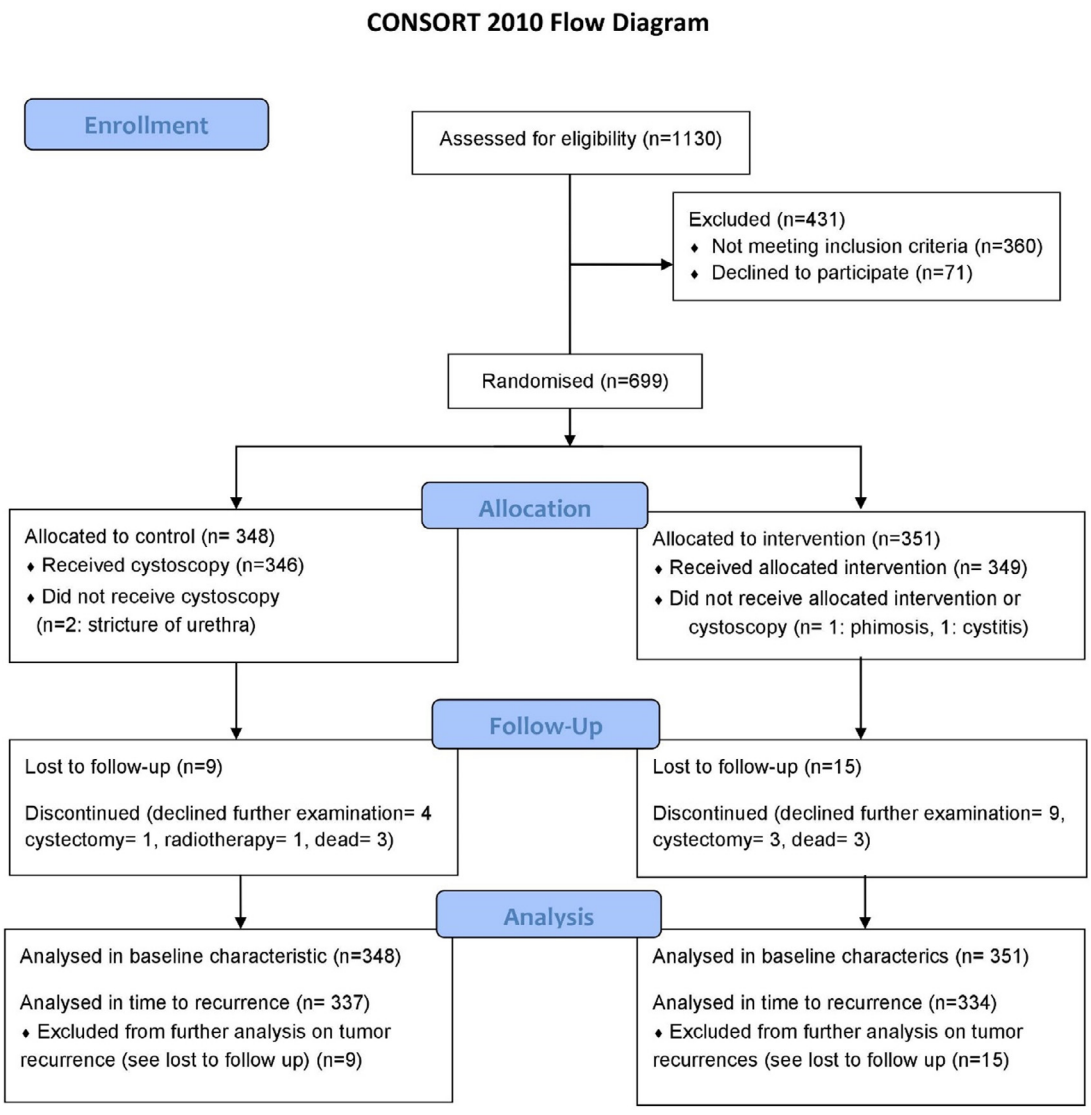

Figure 1. Patient flow chart. (Color version available online.)

comparing the 2 study arms (122 patients in the intervention arm vs 116 in the control arm, P=0.69) (Table 2). Moreover, there was no significant difference in number of false positive findings.

In the control group, 181 patients have had the diagnosis of NMIBC for a median time of 2.93 years and this was similar in the intervention group with 164 patients with a median time of 2.98 years with the diagnosis (Control: range 0.23-32.25 vs Intervention: range 0.07-33.17, $P = .50$). For 167 patients in the control group (23.9%) and 187 patients in the intervention group (26.8%), the diagnosis of NMIBC was only 4 months old and the time of study enrolment was their first surveillance cystoscopy ($P = .16$).

There was a significantly lower recurrence rate in the eight months following randomization in the intervention group compared to the control group. Thus, 117 patients had at least 1 tumor recurrence in the intervention group compared to 143 patients in the control group ($P = .049$). Logistic regression analysis revealed an odds ratio of 0.67 (95% CI: 0.48-0.95 $P = .02$) correlating to a tumor reduction of 33% in favor of the intervention group.

Table 2. Cystoscopy at the time of randomization, *n*: 699

First Follow-up After TURBT (%)	Control	Intervention	*P* Value
Allocation after randomization	348 (49.8)	351 (50.2)	.99
No cystoscopy performed	2 (0.3)	2 (0.3)	
Normal cystoscopy	182 (26.2)	180 (25.9)	.69
Tumor (%)	116 (16.7)	122 (17.6)	.69
Ta LG (%)	87 (12.5)	97 (14.0)	
Ta LG + CIS	1 (0.1)	0	
Ta HG (%)	19 (2.7)	19 (2.7)	
Ta HG + CIS	3 (0.4)	1 (0.1)	
CIS	2 (0.3)	5 (0.7)	
T1a	3 (0.4)	0	
T1b	0	0	
T2	1 (0.1)	0	
False positives (%)	50 (7.2)	50 (7.2)	.46

CIS, carcinoma in situ; HG, high grade; LG, low grade; PDD, photodynamic diagnosis; TURBT, transurethral resection of bladder tumor.

Subgroup analyses regarding the primary endpoint, recurrence within 8 months after randomization, did not reveal any significant findings regarding effect depending on patient risk group or previous TURBT characteristics. The risk of tumor recurrence in the subsequent cystoscopies, were significantly higher in the control group, if there were tumor at the first cystoscopy after TURBT (Control: 82 [73.2%] vs Intervention: 65 [56.5%], *P* value <.008) (Table 3).

Time to first tumor recurrence was significantly longer in the intervention arm compared to the control arm, if findings at the randomization were not included (Fig. 2).

In total, 470 TURBT's in general anesthesia were performed throughout the time of follow-up. The number of TURBT's was higher in the control group compared to the intervention group. This difference was, however, not significant (Intervention, *n*: 210 vs control group, *n*: 260, *P* = .06). If nonmalignant tissue from the TURBT's were excluded from the analysis, leaving 377 procedures in total, the difference between the groups was significant, as 209 TURBT's were performed in the control group compared to 168 TURBT's in the intervention group (*P* = .04). We did not find significant differences in tumor size, risk of tumor progression, nor identification of carcinoma in situ at different time points when comparing patients in the 2 study arms. The majority of tumor recurrences were <0.5 cm and low-grade noninvasive tumors (Table 4). At time of enrolment, 12 patients were diagnosed with CIS (*n*, intervention: 6 vs *n*, control: 6, *P* = .95). Additional 12 patients were diagnosed with CIS later at the subsequent cystoscopies (*n*, intervention: 4 vs *n*, control: 8, *P* = .24).

DISCUSSION

Two meta-analyses, evaluating 12-month follow-up after rigid PDD-TURBT, revealed a significantly reduced recurrence rate in favor of PDD.[1,17] Moreover, a randomized study concluded that fluorescence cystoscopy potentially could reduce tumor recurrence with a high statistical significance for at least 8 years.[18] However, other randomized studies have not been able to show benefit of PDD on reduced recurrence risk.[19,20]

Table 3. Primary endpoint—% risk of recurrence within 8 months from randomization—stratified into risk groups and type of TURBT before study inclusion

	Control	Intervention	*P* Value
All	42.4%	35.0%	.049
Primary tumor at TURBT before randomization	39.2%	48.7%	.54
Recurrent tumor at TURBT before randomization	60.8%	51.3%	.056
Tumor at the time of randomization	73.2%	56.6%	.008
No tumor at the time of randomization	26.8%	43.5%	.42
Low risk	30.9%	43.4%	.86
Intermediate risk	54.8%	45.3%	.14
High risk	14.3%	11.3%	.23
PDD at last TURBT	69.9%	78.6%	.22
No PDD at last TURBT	30.1%	21.4%	.079
MMC at last TURBT	20.3%	25.6%	.63
No MMC at last TURBT	79.7%	74.4%	.06

MMC, Mitomycin C; PDD, photodynamic diagnosis; TURBT, transurethral resection of bladder tumor.

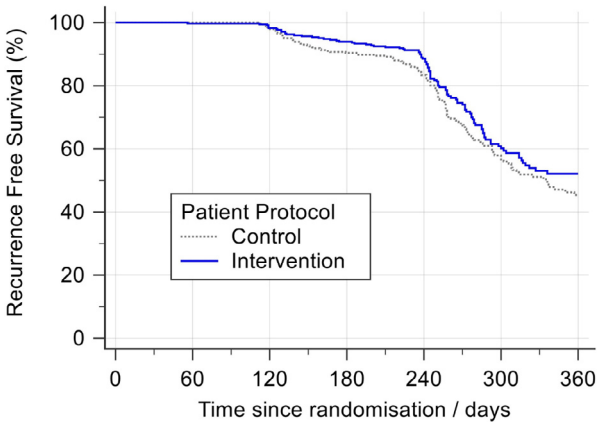

Figure 2. Recurrence-free survival. Recurrences at the time of randomization are *not* included. (Color version available online.)

Two feasibility studies, both published in 2005, concluded that PDD guided flexible cystoscopy is both feasible and at least comparable to rigid PDD cystoscopy.[12,14] Daneshmand et al concluded, that HAL-PDD flexible cystoscopies significantly improve tumor detection, and is considered safe to use during the surveillance setting.[15]

In the current study, we found a statistically significant difference in tumor recurrence in favor of PDD flexible cystoscopy in a routine surveillance cystoscopy setting. We found no differences in tumor sizes, stage progression, nor identification of CIS between the 2 groups. One theoretical explanation to why use of PDD in surveillance can reduce recurrence rate is that early recurrences may arise from small tumors not yet visible at the time of TURBT or residual tumor. By using PDD on the first follow-up visit, tumor detection of these will be improved.[21] However, an interestingly finding in the present study was that there was no difference between the groups regarding overall tumor detection at the first follow-up at the time of randomization, whereas we found a reduced recurrence rate in the remaining follow-up. This is in contrast to the study by Daneshmann et al, where detection was significantly improved in the intervention arm. One plausible explanation for the reduction in subsequent recurrence rate in our study can therefore not be explained by identification of more patients with recurrence at the time of intervention. Instead, it could be a consequence of the fact that by using PDD-guided flexible cystoscopy, it was possible to detect, and treat, small *additional* tumors in patients where recurrence was already found at the time of randomization. However, often 1 or 2 lesions—or suspicious areas—were biopsied and the rest were fulgurated. By doing so, we have not any histopathologic evaluation on the fulgurated lesions to support our hypothesis of additional findings. The coagulation of small lesions in the

Table 4. Number of patients. Tumor size at 8 and 12 months cystoscopy

Tumor size at 8 months cystoscopy							
	<5 mm	5-10 mm	11-20 mm	>20 mm	N/A	Total	*P* Value
Control	61	3	0	0	5	69	.23
Intervention	46	5	0	2	2	55	
Total	107	8	0	2	7	124	
Tumor size at 12 months cystoscopy							
	<5 mm	5-10 mm	11-20 mm	>20 mm	N/A	Total	*P* Value
Control	90	8	1	1	6	106	.85
Intervention	76	7	1	1	2	87	
Total	166	15	2	2	8	193	

N/A, data not available.

bladder that could be considered as false positive by current pathology might have developed into true malignant lesions if left untreated.[22,23] Patients in the intervention group had significantly fewer TURBT's performed throughout the follow-up period compared to patients in the control group, when false positive tumors were excluded from the analysis. As the secondary endpoint was numbers of procedures in general anesthesia, we did not include the procedures performed in the outpatient clinic in this analysis. Unfortunately, in one of the hospitals participating in the study, it was not possible to treat small tumors in the outpatient clinic during the subsequent cystoscopies after the time of the enrolment. Because of that, the total numbers of TURBT procedures in general anesthesia are possibly overestimating the relevant number of procedures, as we would assume, several of the tumor recurrences registered in patients from that particular hospital were most likely feasible for outpatient treatment, if it was possible. We did not enrol patients if they have had BCG intravesical induction treatment in the 4 months between the latest TURBT and study inclusion. The inclusion of all subgroups and these exclusion criteria can explain the low number of CIS detection in the 2 groups.

Consistency of the study design obtained by the same urologist performing all cystoscopies during the time of randomization in both groups, is a strength in terms of reducing interobserver variability.[24] Due to logistics, it was not possible to have the same urologist perform all subsequent cystoscopies throughout the follow-up period after inclusion of the patients in the study. However, this could contribute as an adjustment if any systematic error occurred from the single surgeon approach during the first follow-up cystoscopy. Patients with recurrence detected during inclusion cystoscopy received the following TURBT under the guidance of PDD or WL as well as with or without the use of postoperative single-shot Mitomycin C according to the routine of the participating centers. A limitation of this study, regarding recurrence-free survival, is the different number of cystoscopies, and intervals between these, based on tumor grade and time span since last recurrence. Thus, patients with high-grade tumors are followed every 4 months whereas patients with low-grade tumors without recurrence are scheduled for a cystoscopy 8-12 months later depending on time since the last recurrence. This can introduce a potentially lead time bias to recurrence-free survival. However, all study patients came for a cystoscopy approximately 12 months following the initial TURBT, and therefore 8 months after randomization, irrespectively of grade and recurrence status. Therefore, data regarding the primary endpoint of the study, recurrences within 8 months from randomization, is unaffected by different follow-up intervals. In the present study, we evaluated the use of PDD at the first follow-up after TURBT, and included all eligible patients with previously known NMIBC without recent adjuvant intravesical treatment. Future studies should focus on selected patient groups to evaluate whet all patients will benefit from PDD during follow-up cystoscopies, or if this should be reserved for specific subgroups of patients and at a specific time during surveillance program following the primary diagnosis of NMIBC. Thus, Mogensen et al reported a potential benefit of flexible PDD in identification of CIS in the outpatient clinic following a full course of BCG treatment.[13]

In conclusion, use of PDD in a routine surveillance flexible cystoscopy at the first follow-up after TURBT reduce the risk of later tumor recurrence in patients with NMIBC compared to WL alone.

References

1. Babjuk M, Bohle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol*. 2017;71:447–461.
2. www.cancer.dk/hjaelp-viden/fakta-om-kraeft/kraeft-i-tal/de-hyppigste-kraeftformer/.
3. Herr HW, Donat SM, Reuter VE. Management of low grade papillary bladder tumors. *J Urol*. 2007;178(4 Pt 1):1201–1205. discussion 5.
4. Mogensen K, Christensen KB, Vrang M-L, Hermann GG. Hospitalization for transurethral bladder resection reduces quality of life in Danish patients with non-muscle-invasive bladder tumour. *Scand J Urol*. 2016;50:170–174.
5. Garg T, Connors JN, Ladd IG, Bogaczyk TL, Larson SL. Defining priorities to improve patient experience in non-muscle invasive bladder cancer. *Bladder Cancer*. 2018;4:121–128.
6. Hermann GG, Mogensen K, Toft BG, Glenthoj A, Pedersen HM. Outpatient diagnostic of bladder tumours in flexible cystoscopes:

evaluation of fluorescence-guided flexible cystoscopy and bladder biopsies. *Scand J Urol Nephrol*. 2012;46:31–36.
7. Rink M, Babjuk M, Catto JW, et al. Hexyl aminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: a critical review of the current literature. *Eur Urol*. 2013;64:624–638.
8. Mowatt G, N'Dow J, Vale L, et al. Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: systematic review and meta-analysis. *Int J Technol Assess Health Care*. 2011;27:3–10.
9. Fradet Y, Grossman HB, Gomella L, et al. A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. *J Urol*. 2007;178:68–73. discussion.
10. Kausch I, Sommerauer M, Montorsi F, et al. Photodynamic diagnosis in non-muscle-invasive bladder cancer: a systematic review and cumulative analysis of prospective studies. *Eur Urol*. 2010;57:595–606.
11. Jocham D, Stepp H, Waidelich R. Photodynamic diagnosis in urology: state-of-the-art. *Eur Urol*. 2008;53:1138–1148.
12. Witjes JA, Moonen PM, van der Heijden AG. Comparison of hexaminolevulinate based flexible and rigid fluorescence cystoscopy with rigid white light cystoscopy in bladder cancer: results of a prospective Phase II study. *Eur Urol*. 2005;47:319–322.
13. Mogensen K, Glenthoj A, Toft BG, Scheike T, Hermann GG. Outpatient photodynamic-guided diagnosis of carcinoma in situ with flexible cystoscopy: an alternative to conventional inpatient photodynamic-guided bladder biopsies in the operating theatre? *Scand J Urol*. 2017;51:376–380.
14. Loidl W, Schmidbauer J, Susani M, Marberger M. Flexible cystoscopy assisted by hexaminolevulinate induced fluorescence: a new approach for bladder cancer detection and surveillance? *Eur Urol*. 2005;47:323–326.
15. Daneshmand S, Patel S, Lotan Y, et al. Efficacy and safety of blue light flexible cystoscopy with hexaminolevulinate in the surveillance of bladder cancer: a phase III, comparative, multicenter study. *J Urol*. 2018;199:1158–1165.
16. Dansk BlæreCancer Gruppe D. Nationale kliniske retningslinier for behandling af blæretumorer i Danmark, 2017, http://skejby.net/Webudgaven/Pdf/DaBlaCa_juni_2017.pdf.
17. Yuan H, Qiu J, Liu L, et al. Therapeutic outcome of fluorescence cystoscopy guided transurethral resection in patients with non-muscle invasive bladder cancer: a meta-analysis of randomized controlled trials. *PloS One*. 2013;8:e74142.
18. Denzinger S, Burger M, Walter B, et al. Clinically relevant reduction in risk of recurrence of superficial bladder cancer using 5-aminolevulinic acid-induced fluorescence diagnosis: 8-year results of prospective randomized study. *Urology*. 2007;69:675–679.
19. Stenzl A, Penkoff H, Dajc-Sommerer E, et al. Detection and clinical outcome of urinary bladder cancer with 5-aminolevulinic acid-induced fluorescence cystoscopy: a multicenter randomized, double-blind, placebo-controlled trial. *Cancer*. 2011;117:938–947.
20. Schumacher MC, Holmang S, Davidsson T, Friedrich B, Pedersen J, Wiklund NP. Transurethral resection of non-muscle-invasive bladder transitional cell cancers with or without 5-aminolevulinic Acid under visible and fluorescent light: results of a prospective, randomised, multicentre study. *Eur Urol*. 2010;57:293–299.
21. Burger M, Grossman HB, Droller M, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: A meta-analysis of detection and recurrence based on raw data. *Eur Urol*. 2013;64:846–854.
22. Drejer D, Jensen JB, Bryan RT. Red patches during bladder cancer surveillance: to biopsy or not to biopsy? *Transl Androl Urol*. 2018;7:280–282.
23. Richards B, Parmar MK, Anderson CK, Ansell ID, Grigor K, Hall RR, et al. Interpretation of biopsies of "normal" urothelium in patients with superficial bladder cancer. MRC superficial bladder cancer sub group. *Br J Urol*. 1991;67:369–375.
24. Draga RO, Grimbergen MC, Kok ET, Jonges TN, van Swol CF, Bosch RJ. The quality of 5-aminolevulinic acid-induced photodynamic diagnosis and transurethral resection of bladder tumors: does the urologist play a role? *Urol Int*. 2012;89:326–331.