Efficacy and Safety of Blue Light Flexible Cystoscopy with Hexaminolevulinate in the Surveillance of Bladder Cancer: A Phase III, Comparative, Multicenter Study

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Abbreviations and Acronyms

AE = adverse event
BCG = bacillus Calmette-Guérin
BL = blue light
BLC = BL cystoscopy
BLFC = flexible BLC
CIS = carcinoma in situ
HAL = hexaminolevulinate
PDD = photodynamic diagnosis
PUNLMP = papillary urothelial neoplasm of low malignant potential
TURB = transurethral bladder resection
WLC = white light cystoscopy
WLFC = flexible WLC

Purpose: We compared blue light flexible cystoscopy with white light flexible cystoscopy for the detection of bladder cancer during surveillance.

Materials and Methods: Patients at high risk for recurrence received hexaminolevulinate intravesically before white light flexible cystoscopy and randomization to blue light flexible cystoscopy. All suspicious lesions were documented. Patients with suspicious lesions were referred to the operating room for repeat white and blue light cystoscopy. All suspected lesions were biopsied or resected and specimens were examined by an independent pathology consensus panel. The primary study end point was the proportion of patients with histologically confirmed malignancy detected only with blue light flexible cystoscopy. Additional end points were the false-positive rate, carcinoma in situ detection and additional tumors detected only with blue light cystoscopy.

Results: Following surveillance 103 of the 304 patients were referred, including 63 with confirmed malignancy, of whom 26 had carcinoma in situ. In 13 of the 63 patients (20.6%, 95% CI 11.5–32.7) recurrence was seen only with blue light flexible cystoscopy ($p < 0.0001$). Five of these cases were confirmed as carcinoma in situ. Operating room examination confirmed carcinoma in situ in 26 of 63 patients (41%), which was detected only with blue light cystoscopy in 9 of the 26

Accepted for publication November 5, 2017.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by Photocure ASA, Norway.

ClinicalTrial.gov Identifier NCT02560584.

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† Financial interest and/or other relationship with Photocure.

‡ Financial interest and/or other relationship with Photocure, Merck, FKD, MDxHealth, Cold Genesys, UroGen, Heat Biologics, Roche, Natera and BioCanCell.

0022-5347/18/1995-1158/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1016/j.juro.2017.11.096
Vol. 199, 1158-1165, May 2018
Printed in U.S.A.

(34.6%, 95% CI 17.2–55.7, p <0.0001). Blue light cystoscopy identified additional malignant lesions in 29 of the 63 patients (46%). The false-positive rate was 9.1% for white and blue light cystoscopy. None of the 12 adverse events during surveillance were serious.

Conclusions: Office based blue light flexible cystoscopy significantly improves the detection of patients with recurrent bladder cancer and it is safe when used for surveillance. Blue light cystoscopy in the operating room significantly improves the detection of carcinoma in situ and detects lesions that are missed with white light cystoscopy.

Key Words: bladder neoplasms; neoplasm recurrence, local; carcinoma in situ; cystoscopy; optical imaging

Approximately 75% of bladder cancers present as nonmuscle invasive disease, which is treated initially with TURB. Recurrence is common, often due to incomplete resection as there are inherent limitations in identifying all malignant lesions with WLC alone.[1] Residual tumor can be found in 30% to 44% of resected cases up to 8 weeks after surgery[2–4] and the rate may reach 70% for high grade tumors.[5,6]

Due to the risk of recurrence and progression patients require regular surveillance cystoscopies, usually every 3 to 6 months.[7] This is routinely performed with WLFC using local anesthesia in the office setting.

Diagnostic techniques based on photoactive porphyrins such as HAL aim to improve the detection and resection of nonmuscle invasive bladder cancer. These agents accumulate preferentially in neoplastic tissue, where they induce an accumulation of protoporphyrin IX, which fluoresces when exposed to blue light between 375 and 440 nm.[8,9] This enhances the demarcation between normal and cancerous tissue, enabling improved detection of exophytic tumors and CIS.[10–14] The detection of additional tumors could have a profound impact on future treatment plans while enhanced visualization allows for more complete resection during TURB.[11]

Growing evidence demonstrates the ability of BLC with HAL to increase tumor detection[15] and improve resection during TURB with subsequent decreased cancer recurrence and cost of care.[11,16–20] In Europe for approximately 3 years a flexible PDD videoscope, the D-Light C PDD Flexible Videoscope System (Karl Storz Endoscopy-America, El Segundo, California) with a chip on the tip has been used with HAL. The latter is marketed as Hexvix® in Europe and as Cysview® in the United States. However, to our knowledge no formal clinical study has yet been performed to determine the improved detection of bladder cancer during surveillance using the flexible PDD cystoscope for BLFC with HAL.

We hypothesized that BLC using a flexible cystoscope would have clinical benefits over white light in patients undergoing office based surveillance. The main aim of this prospective, multicenter, phase III study was to compare BLFC with HAL to WLFC in the detection of bladder cancer during surveillance.

MATERIALS AND METHODS

Study Design

This prospective, open label, comparative, within patient, controlled, phase III study was done at 17 centers across the United States. It was performed in accordance with Good Clinical Practice, including ICH (International Conference on Harmonisation) Harmonised Tripartite Guideline E6 and the Declaration of Helsinki as well as title 21 of the United States Code of Federal Regulations, Parts 50, 56 and 312. Written approval was obtained from the relevant institutional review board at each study site and all patients provided fully informed written consent before enrollment.

Patients

Patients with a history of multiple, recurrent or high grade bladder tumors were eligible if they had a tumor that was histologically confirmed by TURB or previous surveillance cystoscopy. Patients who had previously received BCG immunotherapy or intravesical chemotherapy were included in analysis as long as 6 weeks had elapsed since the last treatment.

Surveillance Examination Process

Following screening and enrollment the patients had the first surveillance visit, during which a urine sample was obtained for cytology. After the bladder was emptied HAL in phosphate buffered saline solution (50 ml of 8 mM solution) was instilled in the bladder of all patients and retained for 1 to 3 hours. Patients received intraurethral anesthesia according to institutional practice. After bladder evacuation the number, size and appearance of all suspected malignant lesions were recorded with white light using the described cystoscopy system.

Following WLFC a sealed randomization envelope was opened to see whether the patient would continue in the study. Randomization was done to ensure that a thorough inspection would be made with white light. Patients randomized to continue were inspected again by the same

investigator using blue light (350 to 440 nm) and suspicious lesions were again recorded.

The first 4 patients at each center were classified as training patients. They completed the surveillance visit and then discontinued the study. Training patients and those randomized to discontinue were treated according to standard clinical practice. Cytology results were not used to assess the need for further evaluation in the operating room but they could be used in the treatment of discontinued patients.

Operating Room Examination

Within 6 weeks of the surveillance visit patients in whom recurrence was suspected during surveillance cystoscopy underwent an operating room examination. All patients received another HAL instillation 1 to 3 hours prior to TURB. The bladder was inspected under white and then blue light using a rigid D-Light C PDD System. All suspicious lesions were mapped at each inspection. After the completion of white and blue light inspections biopsies were taken of all suspicious lesions and resection was done according to normal clinical practice.

All biopsies were labelled according to the identification method and were sent for analysis by a local pathologist and a pathology consensus panel using the 2004 WHO/International Society of Urologic Pathology consensus classification[21] and the 2002 TNM classification for staging of bladder cancer.[22] The panel pathologists were blinded to the decision of the local pathologist and the identification method. The consensus panel result was used for assessment of the efficacy end points.

Adverse events were recorded at the surveillance and operating room visits.

Assessments and Statistical Analysis

Based on epidemiological data it was assumed that 35% of the patients examined during surveillance would have visible lesions and be referred for repeat HAL instillation and examination. It was estimated that in 9% of the patients recurrence would be detected only with BL inspection. Including training patients and patients who were randomized out during surveillance approximately 360 had to be enrolled to achieve 100 patients with repeat HAL administration.

The primary efficacy end point was the proportion of patients with histologically confirmed malignancy that was detected only by BLFC and not by WLFC in the surveillance setting. The primary safety end point was the proportion of patients with adverse events following surveillance.

Secondary efficacy end points included the proportion of patients in whom 1 or more CIS lesions were histologically confirmed in the operating room with BLC when none were seen with WLC. The other end point was the proportion of patients in whom additional tumors were seen with BLC in the operating room that were missed with WLC.

A false-positive lesion was defined as a suspected lesion seen on surveillance which was histologically confirmed in the operating room as not malignant (not PUNLMP, CIS, Ta, T1 or T2-T4). The false-positive detection rate was calculated as the total number of patients referred to the operating room with false-positive lesion(s) seen by each method divided by the total number of patients undergoing surveillance.

Summary tables and analysis were prepared with SAS®, version 9.4 or higher.

The primary efficacy analysis was performed in all patients who underwent surveillance cystoscopy and were found to have a histologically confirmed malignancy. The CIS detection end point was performed in all patients with histologically confirmed CIS. Also, the proportion of patients with tumors seen with BLC that were missed with WLC was assessed in all patients with confirmed malignant tumors. False-positive findings were assessed in all patients with available surveillance results. Efficacy end points were analyzed using the exact test for a single proportion with a significance level of 5%.

The population to assess the safety of BLFC with HAL on surveillance was all patients who received HAL instillation during surveillance, including training patients and patients randomized to discontinue the study.

RESULTS

Patients

From September 2016 to January 2017 the study enrolled 304 patients, including 68 training patients (table 1). In 202 of the 304 patients high grade cancer was detected at the last TURB prior to surveillance cystoscopy. The mean number of prior recurrences before study entry was 1.7 (table 1 and fig. 1). Two-thirds of the patients had received BCG or chemotherapy between 6 weeks and 90 days prior to surveillance cystoscopy (fig. 1). Mean HAL retention time was 68.1 minutes.

Tumor Detection

Following surveillance cystoscopy 103 patients were referred to the operating room with suspicion of malignancy based on visual inspection. Malignancy was confirmed in 63 of these patients, including 26 with CIS (fig. 2). In 13 of these 63 patients (20.6%, 95% CI 11.5–32.7) recurrence was seen only with BLFC ($p < 0.0001$), which was confirmed as CIS in 5 (table 2). A tumor was seen with WLFC that was not seen with BLFC in only 1 patient.

At the operating room examination 26 of 63 patients (41%) were confirmed to have CIS, which was detected only with BLC in 9 of the 26 (34.6%, 95% CI 17.2–55.7, $p < 0.0001$, table 2). Four of the 5 patients with CIS who were referred based only on the BLFC inspection had CIS only and no other concurrent tumors (table 3). This was also noted in another 2 patients referred based on WL and BL inspections.

Blue light cystoscopy detected malignant lesions that were missed with WLC in 29 of the 63 patients (46.0%, 95% CI 33.4–59.1, table 2). Table 4 shows the lesion detection rate by lesion type. Only 6 of the 63 patients (10%) with recurrent tumors had

Table 1. *Demographics, and baseline patient and disease characteristics, and adverse events at surveillance examination in 304 patients in surveillance cystoscopy population*

Mean ± SD age/median (range)	69.0 ± 10.40/70.0	(35–92)
No. male (%)	242	(79.6)
No. female (%)	62	(20.4)
No. race (%):		
White	272	(89.5)
Black	29	(6.6)
Asian	10	(3.3)
Other	0	
No. ethnicity (%):		
Hispanic or Latino	6	(2.0)
NonHispanic or Latino	296	(97.4)
Mean ± SD cm ht/median (range)	174.1 ± 9.2/175.0	(145–198)
Mean ± SD kg wt/median (range)	89.7 ± 19.5/87.8	(45–160)
Mean ± SD days since last TURB/median (range)	167.7 ± 201.44/123.0	(22–2,080)
Mean ± SD No. tumors/median (range)*	2.2 ± 2.43/2.0	(0–30)
Mean ± SD No. prior recurrences/median (range)†	1.7 ± 2.03/1.0	(0–12)
No. tumor stage at last TURB (%):‡		
Tx	1	(0.3)
T0	8	(2.6)
Ta	169	(55.6)
T1	52	(17.1)
CIS	100	(32.9)
T2-4	3	(1.0)
No. tumor grade at last TURB (%):		
Benign	11	(3.6)§
PUNLMP	1	(0.3)
Low grade	84	(27.6)
High grade	202	(66.5)
No. AEs	12	
No. pt with any AE (%)	11	(3.6)
Av No. AEs/pt	0.04	
No. related AEs	7	
No. pt with related AE (%):	6	(2.0)
Dysuria	2	(0.7)
Urethral pain	2	(0.7)
Bladder discomfort	1	(0.3)
Erythema	1	(0.3)
Pruritus	1	(0.3)
No. unrelated AEs	5	
No. serious AEs	0	
No. pts with AE causing study (%):		
Procedure interruption or discontinuation	1	(0.3)
Withdrawal	1	(0.3)

* In 299 patients.
† In 300 patients.
‡ Multiple tumor stages in some patients.
§ Stage not reported in 3 patients coded with benign condition by investigators.

positive urinary cytology (table 5). Urinary cytology results were atypical in 17 patients (27%), suspicious in 7 (11%), negative in 29 (46%) and unsatisfactory in 4 (6%).

Table 5 shows the distribution of tumor grade as assessed at TURB before study entry. Of the 13 patients in whom recurrence was identified only with BLFC 6 (43%) had previously been classified with a low grade tumor.

Accuracy

False-positive findings were found in the surveillance setting in 40 of the 220 patients, including 20 (9.1%) using WLFC and the remaining 20 (9.1%) using BLFC.

Adverse Events

During surveillance a total of 12 AEs in 11 patients were recorded in the group of 304 patients. The adverse events believed to be related to the procedure were dysuria, urethral pain, bladder discomfort, erythema and pruritus but none was rated as serious (table 1).

DISCUSSION

In this prospective, phase III study we compared the efficacy and safety of BLFC and WLFC in the detection of bladder cancer during surveillance cystoscopy in the office setting. Secondary objectives were to assess the ability of BLC to detect CIS overlooked by WLC and the ability of BLC to detect tumors in the operating room that were missed with WLC.

The study population was typical of a high risk group with nonmuscle invasive bladder cancer. Of the patients with recurrence 40% were diagnosed with CIS. Interestingly none of the 13 patients detected with recurrence based only on BLFC had positive cytology. Although urinary cytology has high specificity, the sensitivity for high grade disease may not be as high as previously thought, given that WLC was always considered the reference standard. This was observed in the current study.

Of the 13 patients in whom recurrence was detected by BLFC alone CIS was detected in 5 only with BLC at the operating room examination. Moreover, 4 of these 5 patients had no other concurrent tumors which may have been detectable by other methods. This demonstrates that patients with CIS do not necessarily present with other tumors and methods such as BLC (rigid or flexible) are important tools to assist in identification. The randomization process used in this study ensured that the white light inspections would be rigorous.

To our knowledge this is the first study in which time since the last BCG administration was reduced to 6 weeks instead of 90 days. This was done to reflect actual clinical practice. Results demonstrated that BLFC and BLC are safe and effective in patients who recently received BCG.

Our findings are consistent with a number of phase III trials which have demonstrated that 16% to 29% of patients had 1 or more Ta or T1 tumors detected by BLC with HAL and not by WLC.[10,12,13,18] The pivotal phase III study showed that in 16% of patients with Ta or T1 tumors at least 1 additional tumor was detected with BLC using

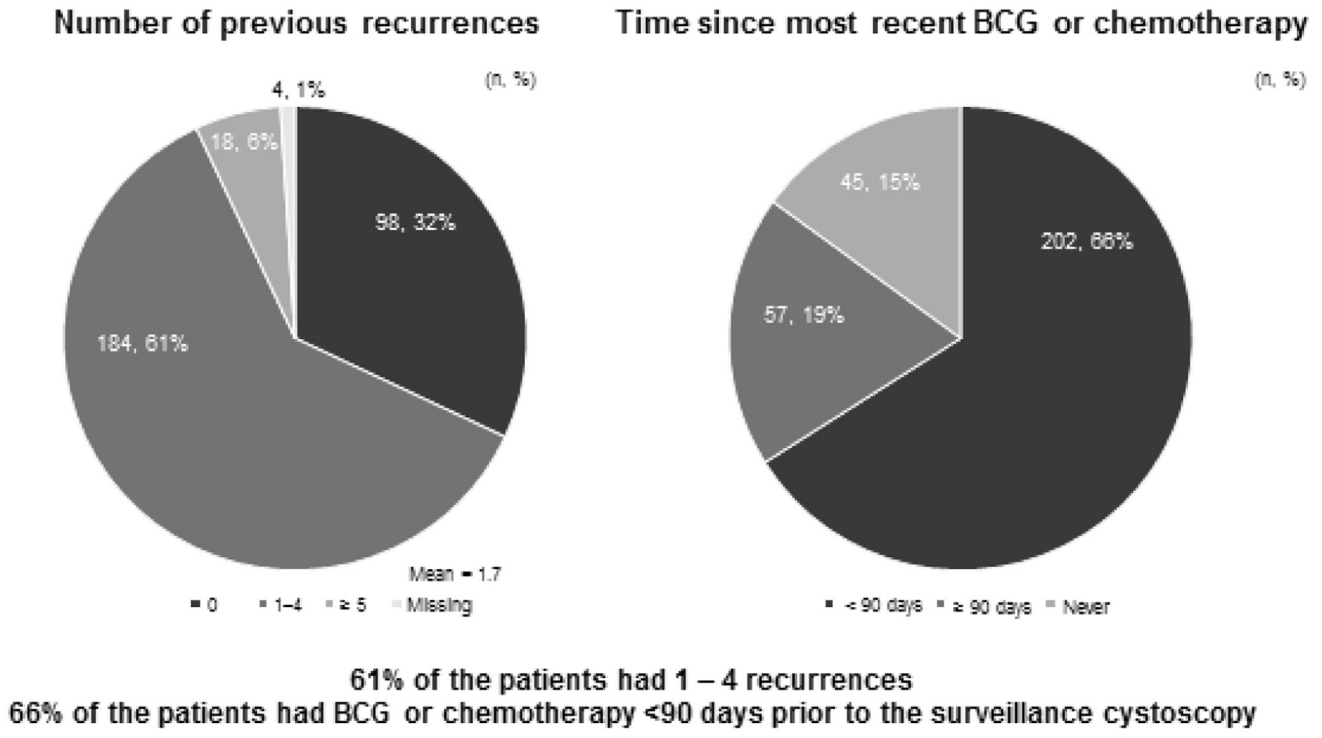

Figure 1. Previous recurrences and BCG or chemotherapy in surveillance cystoscopy population of 304 patients

HAL that was missed by WLC ($p = 0.001$), resulting in a significant reduction of the recurrence rate within 9 months ($p = 0.026$).[12,13,18]

The results of 2 phase III studies demonstrated that BLC with HAL significantly improved the detection of CIS lesions with consequences on patient treatment and potentially improved prognosis.[15] One study included 211 patients with suspicion of known bladder cancer.[15] CIS was found in 39% of evaluable patients, of whom 22% had CIS lesions detected only by BLC with HAL. Data from the other study showed that in 13 of 41 patients CIS was detected only by BLC with HAL ($p < 0.0001$).[11] A small study from 2005 confirmed that flexible

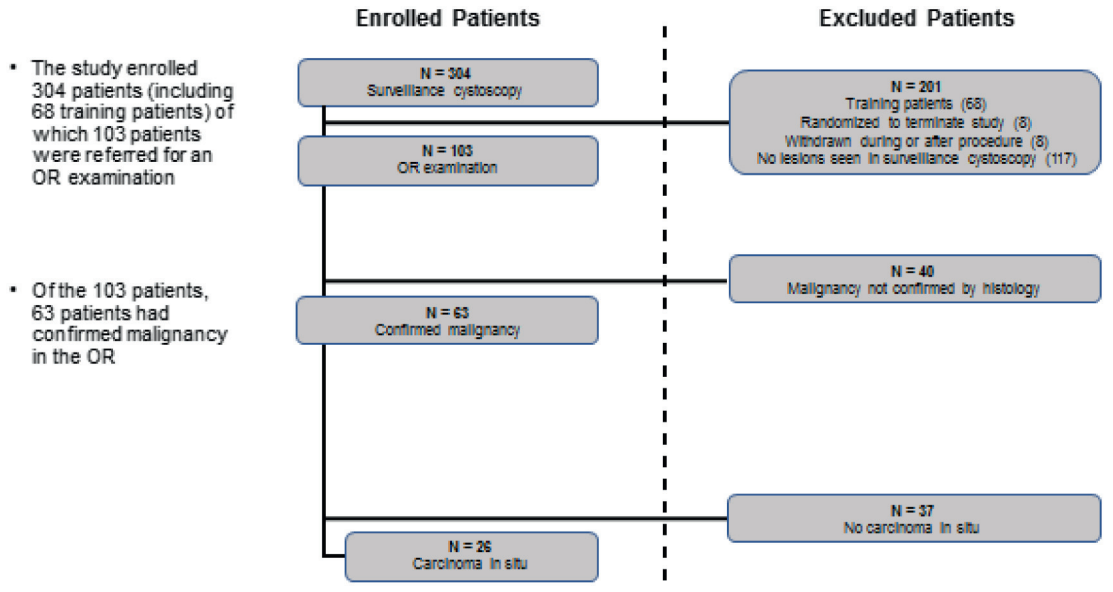

Figure 2. Patient flow. *OR*, operating room.

Table 2. *Detection of recurrence and additional tumors by BLFC and BLC*

	No. Pts (%, 95% CI)
Surveillance examination:	63
Recurrence	63
Recurrence seen only with BLFC	13 (20.6, 11.5—32.7)*
CIS seen only with BLFC	5 (8)
Operating room examination:	63
CIS	26
CIS seen only with BLC	9 (34.6, 17.2—55.7)*
Malignant lesions	63
Additional malignant lesions seen only with BLC	29 (46.0, 33.4—59.1)
Worst tumor type identified by BL, not WL, in pts with additional tumors seen with BLC:	29
CIS	13 (21)
T1	2 (3)
Ta, high grade	2 (3)
Ta, low grade	11 (17)
PUNLMP	1 (2)

* Recurrence seen only with BLFC and CIS seen only with BLC $p < 0.0001$.

cystoscopy was feasible and had results comparable to those of rigid cystoscopy.[23]

Two recent meta-analyses confirmed a significant increase in the detection of papillary tumors and CIS by adding blue light inspection while reducing the rates of residual disease and recurrence at extended followup.[17,18] Cost was also examined in a study which found an initially higher cost for BLC but decreased overall costs since fewer repeat procedures were required, given the decreased recurrence rates.[19] However, overall cost implications are complex and will be the subject of future research.

As a result of this body of literature in support of BLC the current American Urological Association guidelines now recommend its use.[24]

The safety of HAL instillation in the bladder was evaluated in all clinical trials and similar AE profiles were reported in patients who underwent BLC with HAL and those treated with WLC only.[25] The adverse events in our study were consistent with those in previous reports.[26]

In the current series the incidence of false-positive lesions seen only with BLFC on surveillance was 9.1%, the same incidence as for WLFC.

Table 3. *Recurrence grade in patients identified on surveillance*

		No. Referred (finding)	
	No. Pts	BLFC Only	BLFC + WLFC
Referred following surveillance, confirmed recurrent CIS	63	13	50
CIS confirmed in operating room	26	5	21
CIS detected only with BL in operating room	9	4 (CIS only)	2 (CIS only), 2 (CIS + high grade Ta), 1 (CIS + high grade T1)
Recurrence grade:			
Low grade	25	7	18
High/high + low	38	6	32

Table 4. *Lesion detection rate by lesion type in confirmed lesion population of 63 patients*

		No. Detected (%, 95% CI)	
Lesion	No. Pts	BLC	WLC
PUNLMP	3	3 (100, 29.2—100)	2 (67.7, 9.4—99.2)
Ta	94	85 (90.4, 82.6—95.5)	70 (74.5, 64.4—82.9)
T1	10	10 (100, 69.2—100)	7 (70.0, 34.8—93.3)
CIS	43	40 (93.0, 80.9—98.5)	27 (62.8, 46.7—77.0)
T2-T4	5	5 (100, 47.8—100)	5 (100, 47.8—100)

All patients in whom malignancy was suspected during surveillance proceeded to the operating room for histological confirmation regardless of medical history or cytology results. This could possibly have contributed to a higher false-positive rate than that generally encountered in clinical practice. In clinical practice patients with a history of recurrent low grade tumors, representing 7 of the 20 (35%) with BL false-positive findings in our study, might be treated in the office instead of being referred to the operating room.

The detection of additional tumors in the surveillance setting may have profound effects on diagnosis. In addition, it could potentially decrease the progression rate by earlier diagnosis of high risk lesions which would have otherwise been missed by WLC.

In clinical practice the actual outcomes from surveillance will depend on local decision making practices and the availability of operating room facilities. Also, the investigators who participated in this study are experts in bladder cancer and had been using BLC in the operating room setting prior to the study. Therefore, the results may not be applicable to other urologists without experience with BLC.

CONCLUSIONS

Office based blue light flexible cystoscopy with HAL significantly improves the detection of recurrent

Table 5. *Urine cytology results in operating room population and tumor grade at last TURB before surveillance in 103 patients*

		Pos		False-Pos	
	Operating Room	BLFC	WLFC/ BLFC	BLFC	WLFC
No. pts	103	13	50	20	20
Baseline cytology:					
Negative	53 (52)	6 (50)	23 (46)	12 (60)	12 (60)
Atypical	24 (23)	3 (21)	14 (28)	3 (15)	4 (20)
Suspicious	13 (13)	2 (14)	5 (10)	3 (15)	3 (15)
Positive	6 (6)	0	6 (12)	0	0
Unsatisfactory or missing	7 (7)	2 (14)	2 (4)	2 (10)	1 (5)
Pathology at last TURB:					
Benign	2 (2)	0	0	0	2 (11)
PUNLMP	1 (1)	0	0	0	1 (5)
Low grade	31 (29)	6 (46)	13 (26)	7 (35)	5 (25)
High grade	66 (64)	7 (54)	36 (74)	12 (60)	11 (55)
Missing	3 (3)	0	1 (2)	1 (5)	1 (5)

bladder cancer and is safe when used in the surveillance setting. Blue light cystoscopy in the operating room significantly improves the detection of CIS and detects lesions that are missed by WLC. Blue light flexible cystoscopy has demonstrated clinical advantages in patients during surveillance of bladder cancer.

ACKNOWLEDGMENTS

Jude Douglass, Healthcom Partners Ltd, Oxford, United Kingdom, assisted with writing and editing.

APPENDIX

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EDITORIAL COMMENT

It has been known for many years that during cystoscopy and subsequent transurethral resection of bladder tumors a fair amount of tumors and CIS may be missed even in the hands of experienced urologists. In addition to repeat resection, novel filter techniques and other methods, PDD has been proposed to improve the detection rate of bladder tumors and flat lesions to render more patients tumor-free after transurethral tumor resection.

Several studies in recent years were able to prove that PDD increases the detection rate of papillary and flat lesions, leading to a higher tumor free-rate and increased detection of CIS after transurethral resection of bladder tumors. Its true clinical value became apparent when a 16% reduction in the relative recurrence rate at 9 months was demonstrated, which continued to be present at a mean followup of 54 months with a tumor-free period of 16.4 months in the fluorescence group vs 9.6 months in the white light group (references 11 and 16 in article).

At longer followup a tendency toward a decreased cystectomy rate also became apparent in patients who underwent initial PDD guided transurethral resection of bladder tumors. Additional reports confirmed a long-term beneficial effect of initial PDD on tumor progression and even on the outcome of cystectomy.[1]

In contrast to adding PDD to tumor treatment, Daneshmand et al now clearly report the additional benefit of PDD in conjunction with diagnostic flexible cystoscopy during surveillance. But where is the benefit for an added number of tumors seen in each individual patient as well as the increased overall number of patients in whom tumor was detected only with PDD? Is no concomitant treatment possible during such a diagnostic procedure?

Improving the detection rate of tumors and flat lesions, and patients who harbor them, during surveillance cystoscopy might lead to a different treatment strategy in some patients. In PDD guided transurethral resection of bladder tumors the true clinical benefit is measured by recurrence and progression intervals, which become recognizable only after months and years. In contrast, PDD guided surveillance will lead to immediate consequences, including transurethral resection of bladder tumors, office fulguration, intravesical instillation therapy or no treatment at all.

PDD necessitates a different instrument and the instillation of a harmless sensitizer, leading to higher costs. Side effects are minimal and mostly related to additional catheterization. Whether the additional expenses save costs due to a reduction in interventions must still be proved and savings will differ in various health care systems. Cost-effectiveness was calculated when adding PDD to transurethral resection of bladder tumors. Therefore, a similar outcome might be postulated with the addition of PDD to surveillance cystoscopy.

Of course, future studies will have to look at these additional costs and the number of procedures avoided as well as patients and tumor types that benefit most from such an additional diagnostic expenditure. But the presented data clearly show that PDD matters, at least in some patients, when added to the surveillance protocol.

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