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Original Article

Prospective evaluation of blue-light flexible cystoscopy with hexaminolevulinate in non-muscle-invasive bladder cancer

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Objectives

To evaluate the utility of blue-light flexible cystoscopy (BLFC) for surveillance of non-muscle-invasive bladder cancer (NMIBC).

Patients and Methods

Prospective cohort of consecutive patients who underwent office-based BLFC for NMIBC. Clinical information was collected including cystoscopic findings and pathological data.

Results

A total of 322 cases were performed on 190 patients. The mean age was 71 years and 83% were men. The highest stage prior to BLFC was Ta, carcinoma *in situ* (CIS), T1, and T2 in 45.3%, 18.4%, 30% and 2%, respectively. Prior to BLFC, 16.8%, 60.5%, and 16.8% were low grade (LG), high grade (HG), and CIS, respectively. Intravesical bacille Calmette–Guérin and intravesical chemotherapy were used in 54.2% and 18.4%, respectively. White-light cystoscopy (WLC) and BLFC were both normal in 173 (53.7%) of cases. WLC was normal and BLFC was abnormal in 26 (8%) cases. Of these, 15 had office-based biopsy and cancer was detected in 13 (87%; six CIS, four HG Ta, three LG Ta). Both WLC and BLFC were positive in 83 (25.8%) cases and 33% had additional tumours found. Cancer was found in 27 (75%) of WLC+/BLFC+ who underwent office-based biopsy including 19 LG Ta, six HG Ta, and two CIS.

Conclusions

Incorporation of BLFC in clinical practice has potential advantages of finding cancer in cases with normal WLC. BLFC detected additional cancers in 33% of patients with positive WLC and BLFC, which can improve surveillance and performance of office-based biopsy. Further research is needed to determine cost-effectiveness and impact on recurrence rates.

Keywords

blue light flexible cystoscopy, non-muscle-invasive bladder cancer, cancer detection, #uroonc, #BladderCancer, #blcsm

Introduction

Non-muscle-invasive bladder cancer (NMIBC) has a high recurrence and progression rate. These risks depend on stage, grade, prior history of bladder cancer, multiplicity, and tumour size and impact recommendations for management and surveillance [1]. Patients with intermediate- and high-risk disease are recommended to receive either intravesical BCG or intravesical chemotherapy to decrease the risk of recurrence and progression. In order to identify early recurrence and progression, patients with NMIBC undergo intensive cystoscopic surveillance in the outpatient setting [1,2]. Until recently, white-light cystoscopy (WLC) has been the only available modality for surveillance in the USA. While WLC has a high sensitivity for detecting papillary tumours, it has been recognised that there is difficulty detecting

carcinoma *in situ* (CIS) and even some papillary disease [3,4]. The consequence of missing recurrences can be progression of disease and inappropriate management decisions, such as in cases of patients with BCG-unresponsive disease, or invasive disease.

Enhanced cystoscopic techniques such as blue-light (BL) cystoscopy have allowed improvement in detection of bladder tumours in the operating room, with demonstrated reduction in recurrences, as well as change in management due to more accurate risk categorisation [3,5]. The use of BL cystoscopy in this setting is now supported by both the AUA/Society of Urologic Oncology (SUO) guidelines for managing NMIBC and the European Association of Urology (EAU) guidelines [1,2]. As most surveillance is performed with WLC, it was important to determine if BL flexible cystoscopy (BLFC) in the office setting also offered advantages in detection. A 2018 prospective multicentre Phase III clinical study in the USA evaluated BLFC for surveillance of patients with intermediate- and high-risk NMIBC [4]. This study included 304 patients and found an overall increased detection rate of 20.6% using BLFC compared to WLC, including 34.6% increased detection of CIS and a finding of additional malignant lesions in 46%. One limitation of this trial was the evaluation of a cohort with only intermediate- and high-risk disease with one time use of BLFC. There are limited real-world data using BLFC, which is confined to European centres [6]. In the present study, the utility of BLFC was evaluated in a prospective cohort of consecutive patients with NMIBC who underwent BLFC at two major academic high-volume bladder cancer centres.

Patients and Methods

This was a prospective cohort of consecutive patients who underwent office-based BLFC for surveillance of NMIBC. Candidacy for BLFC was based on the 2018 expert consensus statement for use of BL cystoscopy in the office setting [7]. All consented patients undergoing BLFC at each institution were included from May 2018 until August 2019. Demographic and clinical information were collected, including indication for BLFC. The findings for WLC and BLFC were recorded. Information on any subsequent biopsies was also collected, as well as cytology if performed. Positive cystoscopy was defined as cystoscopy identifying lesions highly suspicious for cancer. Negative cystoscopy was defined as cystoscopy where no suspicious lesions were found. Indeterminate cystoscopy was defined based on the provider identifying a lesion that was abnormal but not characteristic of malignancy.

During each cystoscopy, we prospectively documented whether additional lesions were identified during the BLFC that were not seen during the WLC.

Results

There were a total of 322 procedures involving 190 unique patients with a history of bladder cancer who were undergoing surveillance cystoscopy. Most patients were older, Caucasian and male (Table 1). About 40% of the patients underwent more than one BLFC. BLFC was performed at the clinicians' discretion, but most of the patients had a history of high-risk disease with T1 (30%), CIS (18.4%), high grade (HG, 60.5%), prior intravesical BCG (54%), and 70% with recurrent disease (Table 2). The findings at time of cystoscopy with WL and BL are shown in Table 3. Most patients (54%) had a normal WL and BL cystoscopy. The next most common finding was that both the WL and BL cystoscopy were positive (25.8%). Of these patients, 27/83 (33%) had additional lesions only seen on BLFC (Fig. 1). Of the 83 patients, 42 went to the operating room for transurethral resection of bladder tumour (TURBT), 36 had office-based biopsy and fulguration within several weeks, two had delayed office-based biopsy and fulguration and three were monitored, as they had negative cytology and negative CxBladder Monitor urine testing. Most of the patients who had office-based biopsy had low-grade (LG) Ta tumours (n = 19, 53%), but there were six patients with HG Ta and two patients with CIS (Table 3).

There were 26 office-based cystoscopies (8%) with negative WL but positive BL findings. Of these patients, 15 had office-

Table 1 Patients' demographics.

Variable	Value
Procedures statistics, *n* (%)	
Total no. of cases	322 (100)
1st time procedure	190 (59.01)
2nd time procedure	68 (21.12)
3rd time procedure	39 (12.11)
4th time procedure	13 (4.04)
5th time procedure	3 (0.93)
Total no. of unique patients	190
Age, years	
Mean (SD)	71.5 (10.3)
Median (range)	73 (34–96)
Male, *n* (%)	158 (83.2)
Female, *n* (%)	32 (16.8)
Race, *n* (%)	
White/Caucasian	162 (85.26)
Black/African American	3 (1.58)
Asian	9 (4.74)
Hispanic or Latino	9 (4.74)
Other (Specify)	7 (3.68)
Smoking status, *n* (%)	
Never	72 (37.89)
Former	103 (54.21)
Current	15 (7.89)
Bladder cancer (status per procedure), *n* (%)	
Primary	96 (29.81)
Recurrent	226 (70.19)

Table 2 Prior cancer history.

	N (%)
Highest stage (Overall)	
Tx	3 (1.58)
T0	0 (0.00)
Ta	86 (45.26)
T1	57 (30.00)
T2	4 (2.11)
Benign	4 (2.11)
Unknown	1 (0.53)
CIS	35 (18.42)
Highest grade (Overall)	
Unknown	7 (3.68)
LG	32 (16.84)
HG	115 (60.53)
CIS	32 (16.84)
Benign	4 (2.11)
Number of tumours	
Unknown	26 (13.68)
0	65 (34.21)
1	47 (24.74)
2–7	38 (20.00)
≥8	5 (2.63)
'Many'	9 (4.74)
Most recent recurrence	
None prior	57 (30.00)
Within 6 months	36 (18.95)
6–12 months	45 (23.68)
>1 year	52 (27.37)
Has patient received intravesical chemotherapy within last 6 months?	
Prior intravesical chemo (Yes)	35 (18.42)
Prior intravesical chemo (No)	155 (81.58)
Has patient received BCG within last 6 months?	
Prior intravesical BCG (Yes)	103 (54.21)
Prior intravesical BCG (No)	87 (45.79)
Last bladder wash cytology results	
Unknown	10 (5.26)
Normal	112 (58.95)
Atypical	22 (11.58)
Positive	13 (6.84)
Suspicious	3 (1.58)
Unsatisfactory	3 (1.58)
Insufficient	10 (5.26)
N/A	17 (8.95)

based biopsies and seven underwent TURBT in the operating room. A total of eight patients (30.8%) had CIS, eight patients had HG Ta (30.8%), three (11.5%) had LG Ta, and three (11.5%) had benign findings. There were an additional 10 patients with indeterminate WL lesions and positive BL of which two had CIS, one had papillary urothelial neoplasm of low malignant potential (PUNLMP), one had atypia, and three had benign findings.

Cytology results are shown in Table 4. Cytology was considered positive if reported as positive or suspicious. Cytology was considered negative if reported as negative or atypical. Sensitivity for cytology overall, HG, CIS only and LG was 26% (16/61), 30% (14/46), 35% (seven of 20) and 13% (two of 15), respectively. There were two false-positive cytology results (one benign and one PUNLMP). In patients with negative WL and positive BL cystoscopies, cytology was positive in only 18.8% (three of 16).

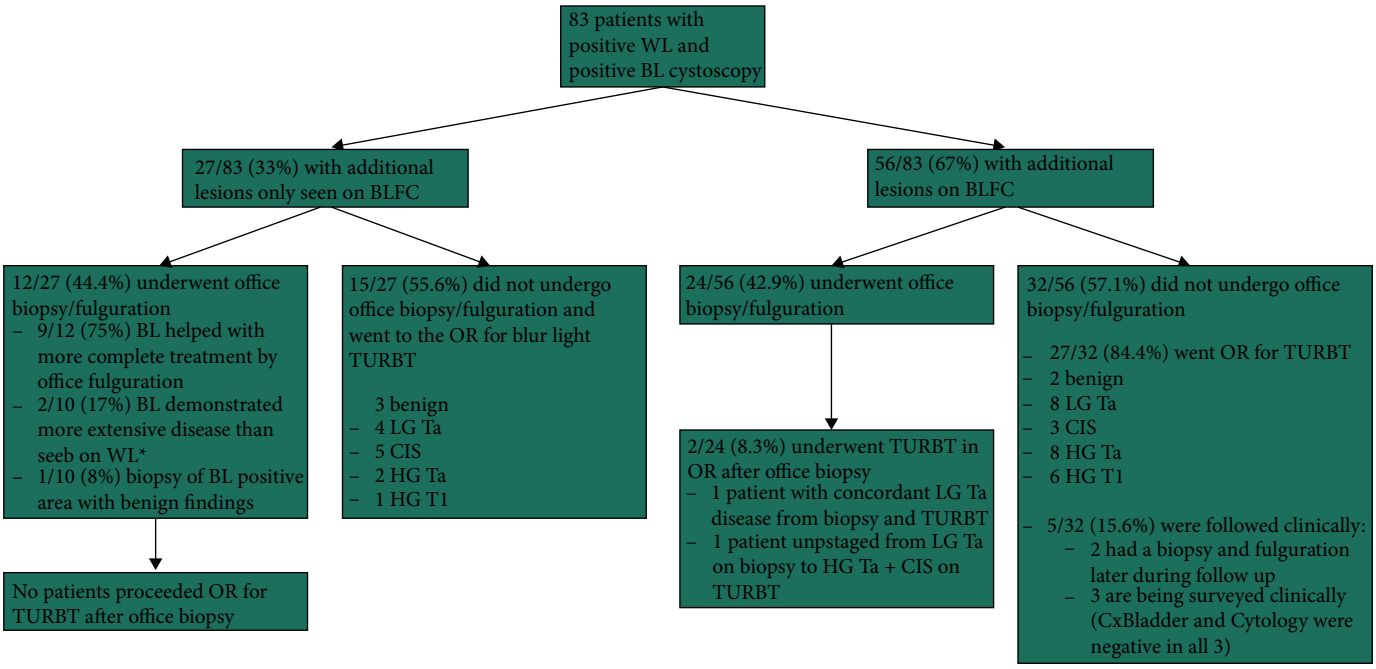
Discussion

This is the first large prospective study in the USA evaluating BLFC in a real-world setting. The potential benefits and ultimately the goal of using BLFC is earlier identification of cancers that would be missed with WLC alone. This can occur in two scenarios including patients who have a positive BLFC in the setting of a normal WLC, and those patients who have a positive WLC but have additional tumours seen with BLFC that change management. In the present study, including 190 consecutive patients undergoing 322 surveillance procedures for NMIBC, 26 procedures (8.1%) had a positive BLFC with normal WLC, and 27 (8.3%) procedures had additional lesions found when both WLC and BLFC were positive. More importantly in patients who had a normal WLC and positive BLFC, 19 of 22 patients who underwent biopsy had cancer including eight patients with CIS and eight with HG Ta tumours. The improvement in detection of CIS is consistent with prior studies both in rigid cystoscopy for patients undergoing TURBT and in the prior BLFC multicentre trial [3,4]. As many patients in our present study had recurrent disease and were receiving treatment with BCG, the identification of CIS is important to assess response to BCG and determine if patients need a change in treatment.

Table 3 Cystoscopy findings and outcomes of office biopsies.

Office cystoscopy findings		*N* (%)	Office biopsy performed	Office biopsy results	TURBT	TURBT pathology
WL	BL					
Negative	Negative	173 (54)	1	1 benign	2	1 benign, 1 PUNLMP
Negative	Positive	26 (8)	15	2 benign, 3 LG Ta, 6 CIS, 4 HG Ta	7	1 benign, 2 CIS, 4 HG Ta
Positive	Positive	83 (25.8)	36	8 benign, 19 LG Ta, 2 CIS, 6 HG Ta, 1 radiation cystitis	42	See Figure 1
Positive	Indeterminate	3 (1)	1	Benign	0	
Indeterminate	Positive	10 (3.1)	3	1 benign, 1 PUNLMP, 1 CIS	4	2 benign, 1 atypia, 1 CIS
Indeterminate	Indeterminate	13 (4)	5	All benign	2	2 benign
Negative	Indeterminate	6 (1.8)	1	Benign	0	
Positive	Negative	2 (0.6)	0		2	1 benign, 1 HG T1
Indeterminate	Negative	6 (1.8)	0		0	

Fig. 1 Follow-up of patients with positive WLC and positive BLFC. * In one patient, biopsy of BL-positive lesion demonstrated CIS, while biopsy of WL/BL-positive lesion demonstrated LG Ta. Both patients proceeded to intravesical chemotherapy. OR, operating room.



For patients who had a positive WLC and BLFC, the finding of additional lesions can be clinically valuable. Of 27 procedures where additional tumours were seen, 12 were performed in the office and 15 in the operating room. For cases going to the operating room, BLFC is useful to detect all lesions during TURBT. For office-based cystoscopy with biopsy and fulguration, detection of all tumours at time of fulguration will prevent these tumours from appearing later, which could avoid future procedures and/or possibly prevent progression of these missed lesions. In fact, office-based biopsy was used predominately for patients with LG Ta cancers in the present cohort precisely to avoid anaesthesia and manage these recurrences less invasively.

One concern with the use of BLFC is the risk of false-positive findings. This occurred in 9% of patients in the Phase III multicentre BLFC study [4]. In the present prospective cohort, three patients who were WL negative and BL positive had benign findings on biopsy. This represents <1% of the entire cohort and two of these biopsies were performed in clinic, which reduces the overall morbidity and cost. There were other false-positive findings with both WL and BL cystoscopies. Among patients with both positive WL and BL cystoscopies there were benign findings in 25% of those who underwent office-based biopsy and 12% of those who went to surgery. Indeterminate lesions are not infrequent in patients with bladder cancer, especially those who undergo multiple TURBTs and intravesical therapy. There were 29 WLC and 22 BLFC that were indeterminate, of which 13 had indeterminate WLC and BLFC. Many of these patients did not undergo a biopsy, so their significance is unclear. However, in cases where WLC was indeterminate and BLFC was positive there were seven patients who had a biopsy of which two had CIS, one had PUNLMP, and four were benign. A previous study evaluating 101 equivocal lesions on office-based cystoscopy found malignancy in 27 patients (26.7%) [8]. It is possible that BLFC can help determine which patients with indeterminate WLC should undergo biopsy, but further studies will be necessary to clarify this issue.

One question is whether BLFC is necessary, as cytology might be able to identify HG disease that was missed by WLC. In the present cohort, cytology only had a 26% sensitivity and in patients with WL-negative and BL-positive cytology had a sensitivity of only 18.8%. Cytology had a sensitivity of only 35% for CIS. These findings are consistent with prior reports that found a lower sensitivity of cytology in contemporary series [9].

There are very few published studies on BLFC. A European multicentre prospective observational study assessed of BLFC

Table 4 Cytology outcomes.

Office cystoscopy findings		*N* (%)	Cytology results	Office biopsy results (cytology result)	TURBT pathology (cytology result)
WL	BL				
Negative	Negative	173 (54)	172/173 148 Normal 11 Atypical 11 Insufficient 2 Positive	1 benign (positive)	• 1 PUNLMP (positive)
Negative	Positive	26 (8)	19/26 11 Normal 4 Atypical 2 Positive 1 Suspicious 1 Insufficient	• 2 benign (NS) • 3 LGTa (1 normal, 2 NS) • 6 CIS (1 positive, 1 suspicious, 2 atypical, 2 normal) • 4 HG Ta (1 positive, 1 normal, 2 NS) • 1 no biopsy (1 atypical)	• 1 benign (1 atypical) • 2 CIS (2 normal) • 4 HG Ta (4 normal) • 2 TUR recommended not done (1 normal, 1 insufficient)
Positive	Positive	83 (25.8)	54/83 28 Normal 11 Atypical 11 Positive 2 Suspicious 2 Insufficient	• 8 benign (6 NS, 2 normal) • 19 LG Ta (15 NS, 3 normal, 1 atypical) • 2 CIS (1 normal, 1 positive) • 6 HG Ta (2 NS, 3 normal, 1 atypical) • 1 radiation cystitis (NS)	• 5 Benign (3 normal, 1 insufficient, 1 NS) • 12 LG Ta (1 positive, 1 suspicious, 5 atypical, 2 normal, 1 insufficient, 2 NS) • 8 CIS (3 positive, 1 suspicious, 1 atypical, 3 normal) • 7 HG T1 (2 positive, 4 normal, 1 NS) • 10 HG Ta (4 positive, 2 atypical, 3 normal, 1 NS) • 5 TUR recommended, not done due to patient preferences and other contraindications (4 normal, 1 atypical)
Positive	Indeterminate	3 (1)	2/3 1 Normal 1 Atypical	• 1 Benign (1 NS)	No biopsies
Indeterminate	Positive	10 (3.1)	10/10 2 Positive 6 Normal 1 Insufficient 1 Atypical	• 1 Benign (1 normal) • 1 PUNLMP (1 Normal) • 1 CIS (1 Atypical)	• 2 Benign (2 normal) • 1 CIS (1 normal) • 1 Atypia (1 normal) • TUR recommended, not done (2 positive, 1 insufficient)
Indeterminate	Indeterminate	13 (4)	10/13 8 Normal 2 Atypical	• 5 Benign (2 NS, 3 normal) • 1 Benign (1 Normal)	• 2 Benign (1 normal, 1 atypical)
Negative	Indeterminate	6 (1.8)	4/6 4 Normal		No biopsies • 1 Benign (1 Insufficient)
Positive	Negative	2 (0.6)	2/2 2 Insufficient	No biopsies	• 1 HG T1 (1 insufficient)
Indeterminate	Negative	6 (1.8)	6/6 4 Normal 2 Insufficient	No biopsies	No biopsies

for surveillance in 69 patients with NMIBC [6]. There were 14 patients with confirmed cancer of which three were found by BLFC only (two Ta and one CIS). There were 11 patients with cancer identified by WLC and BLFC. Our present experience was significantly larger than this study, but we expect further information on utility will be gleaned from the ongoing prospective BL registry.

There are several areas that still need to be evaluated when adopting BLFC that were not directly assessed in the present study. These include some of the downsides of the approach. There is need for the patient to arrive at least 1 h prior to the procedure so the Cysview can be instilled in the bladder. While our clinics had sufficient rooms and manpower for this extra step, it does require a change in workflow and could be an issue if there are space constraints in a clinic. As providers, we did not adjust our clinical volumes, but there is a little added time for each cystoscopy to evaluate the bladder both with WL and BL. There were no reported complications from the instillation and no known adverse reactions, but as this was not a formal trial, the patients were not specifically queried about added complications. It would also be challenging to differentiate side-effects related to the cystoscopy from those related to instillation without a randomised approach.

There are several limitations to the present study. The urologists involved in this study have considerable experience with BL technology and there was no learning curve, which could impact the rate of false-positive results and detection rates. A decision to biopsy or not was determined by the patient and clinician, so some patients were observed and other factors such as prior history, cytology and/or urine markers and patient demographics could have impacted decisions regarding need or urgency for biopsy. However, most of the BLFC patients did undergo biopsy, so confirmation of accuracy was feasible for most patients. The present study was not designed as a longitudinal study and

further work will be necessary to determine if use of BLFC reduce recurrences. A randomised trial would likely be necessary to assess this type of endpoint.

Conclusions

Incorporation of BLFC in clinical practice has potential advantages of finding cancer in cases with normal WLC. WLC was normal and BLFC was abnormal in 26 cases and of those who underwent office-based biopsy, 87% were found to have cancer that was mostly HG. BLFC detected additional cancers in 33% of patients with positive-WLC and -BLFC, which can improve surveillance and performance of office-based biopsy. Further research is needed to determine cost-effectiveness and impact on recurrence rates.

Conflict of Interest

The authors declare the following competing interests: consultancy for Photocure.

Yair Lotan, Siamak Daneshmand also perform research with Storz.

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Abbreviations: BL(FC), BL (flexible cystoscopy); CIS, carcinoma in situ; HG, high grade; LG, low grade; NMIBC, non-muscle-invasive bladder cancer; PUNLMP, papillary urothelial neoplasm of low malignant potential; TURBT, transurethral resection of bladder tumour; WL(C), white-light (cystoscopy).