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Original article

Blue light cystoscopy for the diagnosis of bladder cancer: Results from the US prospective multicenter registry

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Abstract

Introduction: Blue light cystoscopy (BLC) using hexaminolevulinate (HAL/Cysview/Hexvix) has been previously shown to improve detection of non–muscle-invasive bladder cancer (NMIBC). Herein, we evaluated the detection of malignant lesions in a heterogenous group of patients in the real world setting and documented the change in risk category due to upstaging or upgrading.

Methods: Prospective enrollment during April 2014 to December 2016 of consecutive adult patients with suspected or known non–muscle-invasive bladder cancer based on prior cystoscopy or imaging, undergoing transurethral resection of bladder tumor at 9 different referral medical centers. HAL was instilled in the bladder for 1 to 3 hours before evacuation and inspection. Sensitivity and specificity of BLC, white light cystoscopy (WLC), and the combination of both BLC and WLC for detection of any malignancy was reported on final pathology. Number of patients with a change in American Urological Association (AUA) risk category based on BLC findings leading to a possible change in management and adverse events were recorded.

Results: Overall, 1,632 separate samples from bladder resection or biopsy were identified from 641 BLC procedures on 533 patients: 85 (16%) underwent repeat BLC (range: 2–5). Sensitivity of WLC, BLC, and the combination for diagnosis of any malignant lesion was 76%, 91%, and 98.5%, respectively. Addition of BLC to standard WLC increased detection rate by 12% for any papillary lesion and 43% for carcinoma in-situ. Within the WLC negative group, an additional 206 lesions in 133 (25%) patients were detected exclusively with BLC. In multifocal disease, BLC resulted in AUA risk-group migration occurred in 33 (6%) patients and a change in recommended management in 74 (14%). False-positive rate was 25% for WLC and 30% for BLC. One mild dermatologic hypersensitivity reaction (0.2%).

Conclusions: BLC increases detection rates of carcinoma in-situ and papillary lesions over WLC alone and can change management in 14% of cases. Repeat use of HAL for BLC is safe.

Keywords: Bladder cancer; Blue light cystoscopy; Diagnosis; Photodynamic

1. Introduction

Bladder cancer is the fourth most common cancer and the eighth most common cause of cancer-related mortality

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in men from the United States [1]. In 2016, roughly 79,030 new cases were diagnosed including 4.6% of all new cancer cases, and 16,870 deaths in the USA were recorded, equating to 2.8% of all cancer deaths [1]. Although most patients are diagnosed with non–muscle-invasive bladder cancer (NMIBC), recurrence rates remain high even at the lowest grade and stage [2]. These patients are also at risk of progression to MIBC [2]. Hence, improvement in initial staging and optimal management is important to reduce risk of recurrence and progression.

The current standard of care for diagnosis is white light cystoscopy (WLC) and urine cytology. Transurethral resection of bladder tumor (TURBT) is key to establishing the pathologic diagnosis and clinical stage. Complete visualization of the entire bladder and resection of all visible tumors is recommended whenever feasible [3]. The main limitation of WLC is difficulty in identifying all areas of malignancy given the multifocal nature of the disease and the presence of often inconspicuous but significant lesions such as carcinoma in-situ (CIS) [4]. EAU guidelines recommend biopsy of any abnormal looking urothelium, or even random biopsy of normal mucosa in case of positive cytology [5]. Current data suggest that early recurrence in patients with NMIBC may be the result of previously undetected lesions at prior TURBT [6–8].

Blue light cystoscopy (BLC) using hexaminolevulinate (HAL/Cysview/Hexvix) is the most validated technique used today to improve tumor detection. Five prospective multicenter trials with over 1,800 patients have shown that HAL-assisted BLC improves detection of NMIBC [6,9–11]. Current published data includes phase III trials from Europe, US, and Canada, systematic reviews, meta-analyses, and cost-analysis studies [12,13], HAL was approved in EU and US for the detection of non–muscle-invasive papillary cancer in patients with suspected bladder lesions.

Although randomized clinical studies are the backbone of regulatory approval and clinical guidelines, they have limitations in terms of patient population. Here, we report on our experience from the multicenter prospective BLC with Cysview Registry. The core objective of this study was to evaluate the detection of malignant lesions in real world patients and to document the change in risk category due to upstaging or upgrading.

2. Materials and methods

2.1. Study populations

Following IRB approval and informed consent, consecutive patients from 9 different referral centers undergoing TURBT using both blue light (BL) and white light (WL) during cystoscopy and biopsy/resection, were enrolled in a registry starting in 2014. Inclusion criteria included adult (>18 y old) patients with suspected or known NMIBC based on a prior cystoscopy or imaging, patients undergoing repeat resection for restaging or recurrence, and those who had positive urine cytology but no apparent lesion. Exclusion criteria were gross hematuria, porphyria, and known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives, patients who refused catheter insertion, had pure upper tract or prostatic urethral lesions or were lost to follow up. Patients were generally scheduled for BLC at least 6 weeks after any prior bacillus Calmette-Guerin (BCG) immunotherapy or intravesical chemotherapy, as well as previous TURBT.

2.2. Study protocol

The procedure requires instillation of HAL, a photosensitizer, into the bladder, resulting in preferential accumulation of protoporphyrins in rapidly proliferating cells such as malignant bladder tumors. They are subsequently converted to photoactive porphyrins, which emit a red fluorescence under blue light (360–450 nm). HAL is made up of 100 mg hexaminolevulinate hydrochloride mixed with 50 ml of diluent. HAL was instilled via an indwelling catheter 1 to 3 hours before planned TURBT. BLC and WLC were performed using the KARL STORZ D-Light C Photodynamic Diagnostic (PDD) system which enables both WLC and BLC (wavelength 360–450 nm) fluorescence cystoscopy. The procedure began with a cystoscopic examination of the entire bladder under WL and then a repeated examination under blue light. Abnormalities of the bladder mucosa during BLC are characterized by the detection of red, homogenous fluorescence. The margins of the abnormal lesions are typically well-demarcated, in contrast to normal urothelium, which appears blue. Then based on the treatment protocol, the lesions which had been found during WLC or BLC, were resected or biopsied for the pathological evaluations. In some cases, random biopsies from visually normal bladder mucosa had been performed.

2.3. Data collection and analysis

Clinicopathologic data were collected including intraoperative findings with WL and BL, lesion characteristics (flat vs. papillary), location, and size. We considered any severe dysplasia, carcinoma in situ, or T1–4 bladder cancer as a positive result of pathology for malignancy. The anonymized data were entered through the secure registry website into the database. The incremental increased detection rate of BLC over conventional WLC was calculated. False-positive (FP) detection rates were calculated as the number of biopsies where no cancer was found, divided by the total number of biopsies/resections where biopsies were taken in either WL or BL categories. Analysis was performed using IBM SPSS statistics ver. 21. by a single investigator (S.T.B.).

2.4. Outcome measures

The independent variable was the final pathology report of the samples from biopsies/resections. The primary outcome measures included the sensitivity and specificity of BLC, WLC, and the combination of both BLC and WLC for detection of any malignancy reported on final pathology, among all patients and sub-analysis among those who had recently received intravesical therapy. We also recorded the number of patients who had a change in the American Urological Association (AUA) risk category [3] based on findings on BLC leading to a possible change in management. Adverse events (AEs) following HAL instillation were recorded with particular attention to repeat use.

3. Results

3.1. Cohort characteristics

Between April 2014 and Dec 2016, 533 patients entered the prospective registry (Supplementary Fig. 1). Overall, 1,632 separate pathology samples from biopsies or resections have been identified from 641 BLC procedures. Eighty-five patients (16%) underwent repeat BLC with HAL (2–5 total instillations). Mean age was 72 years, and 84% of patients were males. One hundred and forty-eight (28%) patients had primary tumors and 385 (72%) had recurrent tumors; prior intravesical treatments were used in 243 (46%) patients; BCG in 199 (37%); and mitomycin C in 92 (18%). Among 1,632 biopsies, pathologic tumor stages were T0 or not applicable in 925 (56%), Ta in 471 (29%), T1 in 176 (11%), and T2–4 in 60 (4%). CIS was detected in 341 of biopsies (21%), alone or concomitantly with papillary lesions. Pathologic grade of the 1,632 lesions were described as benign or not mentioned in 933 (57%), PUNLMP in 4 (<1%), low grade in 224 (14%), and high grade in 471 (29%). Demographic details are shown in Table 1.

3.2. Detection rates

Using final pathology as the reference standard, the sensitivity of WL, BL, and the combination for any malignant lesion was 76%, 91%, and 98.5%, respectively. The addition of BL to standard WLC increased the detection rate by 12% for any papillary lesion and 43% for CIS (Table 2).

Within the group of WL negative lesions, an additional 206 lesions in 133 (25%) patients were detected exclusively with BL. In patients who had no tumors detected by WLC, malignant lesions were exclusively discovered by BLC in 41 (8%). In multifocal disease, BLC resulted in AUA risk-group upward migration in 33 (6%) patients (Table 3). Thus, the total rate of upgrading or upstaging was 14% using BLC. Change in management in this series was defined as receipt of intravesical therapy when it was not planned, increase in duration of therapy, or proceeding with radical cystectomy.

Table 1
Clinical and pathological characteristics of patients in blue light cystoscopy registry

$N = 533$	N (%)
Median age, y (range)	72 (23–101)
Male	446 (84)
Primary occurrence	148 (28)
Intravesical treatment	243 (46)
BCG	199 (37)
Others	92 (17)
Cytology	
Positive	192 (12)
Suspicious	154 (9)
Pathological stage ($n = 1,632$)	
T0	925 (56)
Ta	471 (29)
T1	176 (11)
T2–4	60 (4)
CIS (alone or concomitant with papillary)	341 (20)
Pathological grade ($n = 1,632$)	
Benign	933 (57)
PUNLMP	4 (0.2)
Low grade	224 (14)
High grade	471 (29)
Cystectomy	49 (9%)

3.3. FP and false-negative rates

Overall FP rate was 25% for WL and 30% for BL. Surgeons who performed more than 10 procedures in the study period had a median WL-FP of 19.6% (interquartile range: 15.2–30.4) and median BL-FP of 27.7% (interquartile range: 20.3–33.7), with significant correlation between WL and BL FP-rates per individual surgeon (Pearson correlation coefficient = 0.78, $P = 0.002$) (Supplementary Fig. 2). Overall false-negative rates in BLC for papillary and flat lesions were 3.8% and 1.8%, respectively. A total of 79 biopsies have been done from areas which were WL and BL negative. Among those samples the rate of malignancy was 0.4%.

3.4. Detection rates in different settings

One hundred and ninety-nine (37%) patients received BCG at least 6 weeks prior to BLC, with a positive

Table 2
Detection rate, positive and negative predictive value of different bladder lesions using white and blue-light cystoscopy

Detection rate (sensitivity)	Any malignancy			Any papillary (%)	Low grade papillary (%)	High grade papillary (%)	CIS (%)
	Sensitivity (%)	PPV (%)	NPV (%)				
White light only	76	64	56	87	86	86	55
Blue light only	91	63	70	91	91	92	91
Either white or blue light	98	59	82	99	99	99	98

NPV = negative predictive value; PPV = positive predictive value.

Table 3
AUA risk category migration due to lesions detected by blue light cystoscopy for non–muscle-invasive bladder cancer among registry patients

Final pathology	Number	AUA risk migration
LG Ta multifocal	14	Low to intermediate
HG Ta	1	Low to intermediate
HG T1	7	Intermediate to high
CIS	11	Low to high (1)
		Intermediate to high (10)

HG = high grade; LG = low grade.

predictive value of BLC-detected malignancy being 55% (Fig). Ninety-five biopsies were taken from margins of a previous resection site (with more than 6 wks' interval), and the positive predictive value of BLC was 52% for malignancy (FP = 31%) (Fig).

Among patients with positive or suspicious cytology within 8 weeks of BLC who had no lesions seen with WLC (111 total), BLC detected an additional 58 malignant lesions in 36 patients (sensitivity 97%). On the other hand, in patients who had negative cytology and no lesions with WLC (150 total), BLC was able to detect 35 new malignant lesions (sensitivity 83%).

3.5. Complications and AEs

AE data was obtained on follow up of 629 BLC procedures. Eighteen patients (2.9%) had minor complications after HAL instillation, including bladder pain (8), and urinary tract pain (12). None were definitively attributable to HAL. There was 1 mild dermatologic hypersensitivity reaction (0.2%).

3.6. Cystectomy

Forty-nine patients (9.3%) eventually underwent radical cystectomy and urinary diversion. The indications for cystectomy were detection of T2–4 (14), recurrent multifocal HGT1 ± CIS (22), and BCG unresponsive CIS (13). Four of the cystectomies (8%) were performed exclusively because of findings detected by BLC (1 due to T2–4, 2 due to HGT1, and 1 due to CIS).

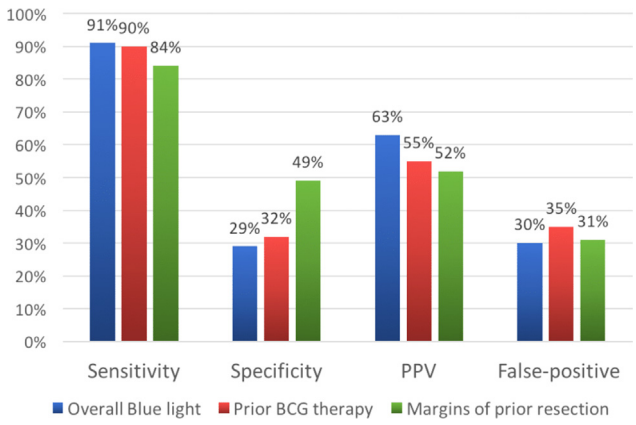

Fig. Detection rate of BLC after BCG therapy and at the margins of a prior resection. (Color version of figure is available online.)

4. Discussion

Results of this prospective, multicenter registry from the United States confirm that BLC with HAL improves detection rates of any malignancy by 23%, papillary lesions by at least 12%, and CIS by 43%, over conventional WLC. Within the WL negative group, use of BLC resulted in detection of additional lesions in 25% of patients. In multifocal disease, BLC resulted in a change in recommended management in 14% of patients. Furthermore, 8% of cystectomies were performed due to upstaging or increase in AUA risk category with lesions detected exclusively by BLC. Use of HAL is very safe with no adverse reactions, including with multiple repeat use.

Several prior randomized controlled studies have shown that BLC with HAL facilitates the detection of bladder tumors [4–8]. Stenzl et al. in their large international RCT showed that among the Ta/T1 group, in 16% of patients at least one of the tumors was detected only with BLC-HAL. Grossman et al. [5] found in their RCT that additional lesions could be detected by BLC in each stage of bladder cancer over WLC . They concluded that at least 1 more tumor was detected by BLC in 29% of patients. Jocham et al. found 19% overall improved detection rates with BLC, which was more prominent in CIS (27%) and dysplasia (49%). This is in line with the overall additional detection rate of 25% in our study. Fradet et al. [4] used BLC for the detection of CIS, and reported that 41.5% more CIS lesions were found by BLC. Finally, Hermann et al. reported that WLC left residual tumors undetected in 49% of patients that were identified by BLC. These rates are also consistent with the 43% additional detection rate of CIS in this study [6].

In our prospective cohort, within the WL negative group, BL was able to detect additional lesions in 25% of patients. This included the 8% population in whom new malignant lesions were exclusively discovered by BLC. Kausch et al. showed in their systematic review of 13 trials, half of which were done with BLC with HAL, that 20% more patients were detected with BLC with HAL in all patients with non–muscle-invasive tumors and 39% more patients among the CIS population.

Any change in tumor grade from low to high was considered upgrading and any increase in tumor stage (from PUNLMP to any T, from Ta to CIS/T1, CIS to T1, ≥T2 stage) was regarded as upstaging. In order to better stratify and prognosticate outcomes, several groups have developed risk groups for NMIBC including the European Organization for Research and Treatment of Cancer (EORTC) and the AUA. In the most recently published AUA guidelines, NMIBC disease is categorized as low, intermediate, or

high-risk in order to aid clinicians in appropriate management [3]. Our study showed that in multifocal disease, BLC resulted in a change in AUA risk category in 6% of patients. This, together with 8% newly diagnosed lesions by BLC, resulted in a 14% change in recommended management of patients. Similarly, Jocham et al. found in their prospective multicenter trial that 17% of patients received more appropriate therapy due to BLC. In our study, 8% of cystectomies were performed due to lesions detected exclusively by BLC.

The FP rate of WLC (30%) was similar to that of BLC (25%) although there was significant variability among surgeons. Kausch et al. [14], in their earlier systematic review showed that the FP rate among trials with BLC-HAL was 11% to 37% for BLC and 9% to 31% for WLC, consistent with our observation. The possible increase in biopsy of false positive lesions with BLC is balanced by increased detection of cancerous lesions and the unmeasured lack of biopsy of equivocal lesions on WLC.

There has been some controversy about which side-effects are attributable to BLC-HAL. Clearly the majority of adverse effects following BLC can be attributed to the TURBT. True adverse drug reactions to HAL are extremely rare. We observed a 2.8% overall complication rate, with a single case of a mild hypersensitivity reaction.

At least 5 systematic reviews and meta-analyses have been performed between 2012 and 2016 reporting long term outcomes of BLC with regard to recurrence and progression of disease [9–15]. Compared to WLC, BLC with HAL was associated with lower 12-month recurrence rates [4]. A lower recurrence rate and improved recurrence-free survival has also been reported for BLC at 1 and 2 years [13]. More recently, Gakis et al. [10] showed in their meta-analysis that in BLC-HAL patients, the rate of progression was significantly lower than those who underwent WLC alone . Also, Kamat et al. [11] revealed a trend toward a lower rate of progression and significantly prolonged time to progression in BLC-HAL patients, particularly in those progressing from Ta to CIS .

Limitations of this study include lack of randomization and possible observation bias. In addition, we did not report any recurrence data. The variation in FP rates in WLC and BLC may be interpreted as lack of consistency among study sites given the lack of concrete objective criteria for assignment of a blue light positive lesion. The aim of this study was to report on the detection of malignant lesions in a heterogenous and diverse group of patients in a real world setting and to document the change in risk category due to upstaging or upgrading. Effort aimed at documenting disease recurrence, progression, recurrence-free, and overall survival are under way with further follow up in the registry.

5. Conclusion

BLC significantly increases detection rates of CIS and papillary lesions compared to WLC alone and can result in upstaging or upgrading in about 14% of patients. Repeat use of HAL for BLC is safe.

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Blue light cystoscopy with Cysview Registry Group

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.urolonc.2018.04.013.

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