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Original article

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

Siamak Daneshmand, M.D.[a,*], Soroush T. Bazargani, M.D.[a], Trinity J. Bivalacqua, M.D., Ph.D.[b], Jeffrey M. Holzbeierlein, M.D.[c], Brian Willard, M.D.[d], Jennifer M. Taylor, M.D., M.P.H.[e], Joseph C. Liao, M.D.[f], Kamal Pohar, M.D.[g], James Tierney, M.D.[h], Badrinath Konety, M.D., M.B.A.[i], and the Blue Light Cystoscopy with Cysview Registry Group

[a] *Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA*
[b] *The James Buchanan Brady Urological Institute, Johns Hopkins University, Baltimore, MD*
[c] *University of Kansas, Kansas City, KS*
[d] *Carolina Urology Partners, Lexington, SC*
[e] *Michael E. DeBakey VAMC, BCM, Houston, TX*
[f] *VA Palo Alto Health Care System, Palo Alto, CA*
[g] *Ohio State University, Columbus, OH*
[h] *Charleston Area Medical Center, Charleston, WV, USA*
[i] *University of Minnesota, Minneapolis, MN*

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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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* Corresponding author. Tel.: +1-323-865-3700; fax: +1-323-865-0120.
E-mail address: daneshma@med.usc.edu (S. Daneshmand).

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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.).