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Das, Sanjay
Gu, Lin
Eve, Claire
et al.

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The Impact of Blue Light Cystoscopy Use Among Nonmuscle Invasive Bladder Cancer Patients in an Equal Access Setting: Implications on Recurrence and Time to Recurrence

Das Sanjay[1,4,6], **Gu Lin**[1,2], **Claire Trustram Eve**[1], **Joshua Parrish**[1], **Amanda M. De Hoedt**[1], **Chad McKee**[3], **William Aronson**[6,8], **Stephen J. Freedland**[1,4,5], **Stephen B. Williams**[1,7]

[1]Department of Surgery, Durham Veterans Affairs Health Care System, Durham, NC

[2]Department of Surgery, Duke Cancer Institute Biostatistics Shared Resource, Durham, NC

[3]Medical Affairs, Photocure Inc., Princeton, NJ

[4]Division of Urology, Cedars-Sinai Medical Center, Los Angeles

[5]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA

[6]Department of Urology, University of California – Los Angeles, Los Angeles, CA

[7]Department of Surgery, Division of Urology, The University of Texas Medical Branch, Galveston, TX

[8]Deaprtment of Surgery, Urology Section, Greater Los Angeles Veterans Affairs, Los Angeles, CA

Abstract

There is a lack of real-world data examining bladder cancer outcomes following BLC. We evaluated 378 NMIBC patients in an equal access setting for differences in bladder cancer outcomes following BLC compared to white light alone. We found BLC significantly reduces recurrence risk compared to white light alone with no difference in outcomes by Black vs. White race.

Address for correspondence: Stephen B. Williams, MD, MBA, MS, Division of Urology, The University of Texas Medical Branch, 301 University Blvd, Galveston, TX 77555, stbwilli@utmb.edu.

CRediT authorship contribution statement

Sanjay Das: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Lin Gu:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Claire Trustram Eve:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Joshua Parrish:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Amanda M. De Hoedt:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Chad McKee:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **William Aronson:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Stephen J. Freedland:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Stephen B. Williams:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Disclosure

Stephen Williams is a consultant for Photocure, Inc.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.clgc.2023.04.011.

Introduction: Prior studies suggest that white light cystoscopy (WLC) alone can fail to detect cases of non-muscle invasive bladder cancer (NMIBC) vs. blue light cystoscopy (BLC). We describe bladder cancer outcomes and the impact of BLC among NMIBC patients in an equal access setting.

Materials and Methods: We assessed 378 NMIBC patients within the Veterans Affairs system that had a CPT code for BLC from December 1, 2014 to December 31, 2020. We determined recurrence rates and time to recurrence prior to BLC (ie, after previous WLC if available) and following BLC. We used the Kaplan-Meier method to estimate event-free survival and Cox regression to determine association between BLC and recurrence, progression, and overall survival; and further, whether these outcomes differed by race.

Results: Of 378 patients with complete data, 43 (11%) were Black and 300 (79%) White. Median follow-up was 40.7 months from bladder cancer diagnosis. Median time to first recurrence following BLC was longer vs. WLC alone (40 [33-NE] vs. 26 [17–39] months). Recurrence risk was significantly lower following BLC (Hazard Ratio [HR] 0.70; 95% Confidence Interval [CI], 0.54–0.90). There was no significant difference in recurrence (HR 0.69; 95% CI, 0.39–1.20), progression (HR 1.13; 95% CI, 0.32–3.96), and overall survival (HR 0.74; 95% CI, 0.31–1.77) following BLC by Black vs. White race.

Conclusion: In this study from an equal access setting in the VA, we observed significantly decreased recurrence risk and prolonged time interval to recurrence following BLC vs. WLC alone. There was no difference in bladder cancer outcomes by race.

Keywords

Cysview; Progression; Bladder cancer; Non-muscle invasive; Blue light; Outcomes

Introduction

Bladder Cancer is the sixth most common type of cancer in the United States and is estimated that there will be 81,180 new cases with approximately 17,100 dying of this disease in 2022.[1] Of newly diagnosed bladder cancer cases, approximately 75% are non–muscle-invasive bladder cancer (NMIBC). One Since its FDA approval in 2010, Blue Light Cystoscopy (BLC) has become an important clinical procedure for bladder cancer management, especially as research suggests that BLC can reduce recurrence rates compared to White Light Cystoscopy (WLC). Two to four However, there is currently a lack of real-world data evaluating the risk of bladder cancer recurrence and progression in an equal access setting, and by race, among those treated with BLC. There is substantial evidence demonstrating that WLC can fail to detect cases of NMIBC as compared to BLC. As a result, those carcinoma in-situ and high grade papillary tumors that remain unidentified can potentially progress to a higher stage and lead to more aggressive interventions, including chemotherapy and need for cystectomy.[5,6] Thus, less effective surveillance using WLC alone may result in missed diagnoses and thus progressive disease, ultimately leading to inferior oncologic outcomes. The primary objective of this study is to assess the impact of BLC with Cysview on recurrence and progression in an equal access setting. We hypothesize that BLC will show decreased recurrence, longer time to recurrence outcomes

than WLC alone, and that these outcomes will not vary significantly by race within an equal access setting.

Materials & Methods

Data Source

Using inpatient data, outpatient data, and fee-basis claims (ie, care provided outside the VA system for which the VA paid), we queried data from the VA Informatics and Computing Infrastructure to identify patients with bladder cancer who underwent BLC from December 1, 2014 to December 31, 2020. The study was approved by the institutional review board at the Durham VA Health Care System, Durham, North Carolina.

Study Cohort

The study population consisted of patients with pathologically confirmed NMIBC at transurethral resection of bladder tumor (TURBT) who underwent BLC on or before December 31, 2020 and had at least 1 year of continuous follow-up within the VA after their BLC. Patients were excluded if they had no bladder cancer diagnosis, had muscle invasive bladder cancer at time of initial diagnosis, or did not receive a BLC. We identified a total of 603 bladder cancer patients who had a Current Procedural Terminology (CPT) code indicating receipt of BLC (CPT A9589 and C9738). Of these, we preferentially selected 442 patients with earliest BLC dates—thus likely to have longer follow-up times—to undergo chart review to confirm that the patients met study eligibility criteria. Ultimately, 378 patients were included in the analysis. 2018 was the earliest date that a BLC was identified using CPT codes within the VA; however, patients were included in this study who received BLC earlier than 2018 from outside the VA.

Study Definitions

Overall recurrence was defined as the first recurrence after diagnosis. WLC recurrence was defined as the first recurrence after WLC but prior to BLC with index date being date of diagnosis from the initial WLC. Of these, patients who did not recur prior to BLC were censored. BLC recurrence was defined as the first recurrence after BLC with the index date being date of BLC. Patients who did not recur after BLC until the most recent follow-up date were censored at the date of most recent follow-up.

Statistical Analysis

Patient disease characteristics and demographic details were summarized across all patients. Kaplan-Meier curves were created to represent the time to bladder cancer recurrence, progression, and overall survival from the time of initial WLC and time from BLC.

A Cox proportional hazards regression model was used to determine the association between the outcomes of interest (recurrence, progression, and survival) and covariates including age at bladder cancer diagnosis, sex, race (non-Black vs. Black), location of BLC procedure (at a VA center vs. at an outside facility), smoking status (ever vs. never), clinical grade, and type of treatment received. All statistical tests were 2 sided, and all analyses were performed using SAS, version 9.4 (SAS Institute Inc). Statistical significance was defined as $P < .05$.

Results

Patient demographics and clinical characteristics are summarized in Table 1 Of the 378 patients included in the analysis, 373 (98.7%) were male and 5 (1.3%) were female. The median age at bladder cancer diagnosis was 71 (interquartile range [IQR], 65–75], and median follow-up time was 40.7 months (3.4 years) from initial bladder cancer diagnosis. The median follow-up time after BLC was 30.4 months (2.5 years) There were 300 (79.4%) and 43 (11.4%) White and Black patients, respectively. Smoking status included “never” in 84 (22.2%) patients, “former” in 197 (52.1%), and “current” in 97 (25.7%). There were 140 patients whose bladder cancer was diagnosed with BLC and 238 were diagnosed with white light. All patients had BLC, with 351 (92.9%) of patients receiving their BLC at a VA center. There were 194 (51%) patients with either TaHG or T1 without CIS; 52 (14%) had CIS with or without TaHG or T1; and 127 (34%) had TaLG only. Of all patients, 39 (10.3%) had disease progression. A total of 239 (63%) patients received BCG at any time point during the study.

A total of 227 (60%) patients had bladder cancer recurrence (Table 2). Of these, 136 (36.0%) had recurrence after BLC, with 56 (24.1%) of these of patients having recurrence prior to and after BLC and 80 (21.2%) had recurrence only after BLC. Of these, 47 patients were diagnosed with NMIBC by BLC. Median time to first recurrence following BLC was longer compared to WLC alone (40 [33-NE] vs. 26 [17–39] months). The recurrence-free rate was also longer following BLC compared prior to WLC (37% [23–59] vs. 27% [21–35] at 60 months estimated). The risk of recurrence was significantly lower following BLC (Hazard Ratio ([HR], 0.70; 95% Confidence Interval [CI], 0.54–0.90) as shown in Fig. 1.Progression and overall survival are shown in Supplemental Fig. 1–2. BLC was not associated with bladder cancer progression. Further, only advanced age at diagnosis associated with worse overall survival (HR, 2.70; 95% CI, 1.84–4.05). Age was associated with a significantly increased risk of overall recurrence (HR, 1.29; 95% CI, 1.10–1.53), recurrence after WLC only (HR, 1.38; 95% CI, 1.12–1.71), and after BLC (HR, 1.35; 95% CI, 1.09–1.69) (Supplemental Tables 1–3).

A total of 39 (10.3%) patients had progression of their bladder cancer with median time to progression not reached. Increased risk of progression was associated with age (HR, 2.50; 95% CI, 1.57–4.14), Cis with or without TaHG or T1 (HR, 10.341; 95% CI, 3.41–31.40), TaHG or T1 with or without Cis (HR, 2.75; 95% CI, 1.06–7.16), cystectomy (HR 66.11, 95% CI, 22.87–191.09), intravesical chemotherapy (HR, 2.77; 95% CI, 1.24–6.18), and systemic chemotherapy (HR, 74.45; 95% CI, 19.90–278.54). BC diagnosed in a VA center was associated with decreased risk of progression (HR, 0.30; 95% CI, 0.11–0.84). There was no difference in progression based on race, smoking status, or receipt of BCG treatment (Supplemental Table 4). There were 52 deaths during the study period. Age at diagnosis was the only significant predictor for decreased overall survival (HR, 2.70; 95% CI, 1.84–4.05) (Supplemental Table 5).

Discussion

Since its FDA approval in 2010, BLC is increasingly utilized clinically as it improves the detection rate of NMIBC by up to 43%.[7,8] This is especially important because WLC alone can fail to detect up to 20% of bladder cancer lesions.[9] However, there has been conflicting evidence of whether BLC also leads to reduced recurrence and progression.[2–4,10] Currently, mitigating recurrence is an unmet need for NIMBC patients, as upwards of 60% of these patients have recurrent bladder cancer within 1 year.[11] In an equal access setting, we found that the risk of bladder cancer recurrence was significantly lower in patients following BLC than WLC alone. These data suggest that BLC may be better than WLC in reducing bladder cancer recurrence risk, which supports current AUA/SUO guidelines recommending BLC usage in patients with NMIBC to increase detection and decrease recurrence.[12].

It is well established that accessibility of healthcare services is an important driver of bladder cancer outcomes. We describe for the first time BLC use in the largest equal access healthcare system in the US: the VA. We found that recurrence rates were 30% lower and there was a longer time to recurrence following BLC compared to WLC alone. The recent PHOTO trial found BLC did not reduce recurrence rates compared to WLC at 3 years.[13] However, the population assessed in that study were largely intermediate risk NMIBC (88%) that did not consistently receive BCG treatment which may limit the impact of these findings. This contrasts the present study where most patients (65%) had high-risk NMIBC and were treated with BCG. The lower recurrence rates we observed in the present study are similar to a recent Cochrane review that found BLC may reduce the risk of disease recurrence compared to white light by 34% in an aggregate analysis of 2994 patients across 15 randomized trials (HR, 0.66; 95% CI, 0.54–0.81).[14] Taken together, our findings suggest that BLC may not only decrease rates of recurrence but have a longer time interval to recurrence. This may have a substantial downstream impact on further diagnostic and therapeutic options for these patients aside from improved recurrence and, as such, may result in significant cost savings, though this requires further study.

Racial disparities in bladder cancer care exist and have been largely attributed to differences in socioeconomic status and access to care.[15,16] Black patients have been shown have worse bladder-cancer specific survival than all other racial/ethnic groups.[16] Though there is robust research that shows that Black patients have higher grade disease and worse disease-specific survival, there is a lack of data examining outcomes after BLC by race[17,18] given that BLC has shown to reduce progression, recurrence, and improve overall survival, we assessed whether oncological outcomes were different among black patients compared to White patients in our cohort. Within the largest equal-access health care system in the United States, we found no significant difference in recurrence, progression, or survival following BLC between Black and White patients with NMIBC. Yet, given the wide HRs between these groups, whether our findings are due to the equal access nature of the VA thereby reducing disparities or limited power to detect such differences is unknown. Ultimately, larger studies are needed to confirm our findings.

Our findings must be interpreted within the context of the study design. First, this was a retrospective study within an equal-access health care system and the results may not

be generalizable. Second, participants may have received care outside the VA system that was not documented in their medical record and thus, was not captured in this analysis. At the same time, hand review of charts may have improved the accuracy and comprehensiveness of our data compared to prior claims-only studies. Third, our cohort was limited in the number of Black patients, though this still higher than most relevant randomized trials.[14] This limited our power for detecting modest associations[9,14,19] with our wide HRs—particularly for progression—we cannot exclude differences in outcomes. Though none of the outcomes were statistically significant by race, future larger comparative studies are needed to confirm our findings. Fourth, not all patients had a previous WLC prior to BLC, causing some selection bias. We did not stratify our analysis based on a prestudy WLC, thus there may be different outcomes between patients who received a BLC without a previous history of WLC and patients who received a BLC with a history of WLC. Fifth, we were limited in controlling for treatments given after BLC diagnosed recurrence. It is likely that patients with more rapid recurrences may be preferably scheduled for BLC; however, we only captured the first occurrence of each treatment and were unable to control later treatments. Sixth, as this was an observational study, we cannot control for selection bias which may impact our findings. For example, some patients may have received BLC without previous recurrence, which is not routine. Finally, race was mostly self-reported in the current study, given that race is a social construct and that our study was retrospective in nature. This is important because race is often used as a proxy for social factors; and as our study utilized a homogenous cohort with respect to equal access to care, our findings are timely given increased focus on access to care as we cross the quality chasm.[20,21]

Conclusion

In the present study, we report the recurrence, progression, and overall survival of patients with NMIBC receiving BLC within the VA health system. We found a significant decrease in risk of recurrence following BLC utilization compared to WLC alone. Moreover, there was no difference in any bladder cancer outcomes by race, which suggests benefits of equal access to care, but should be interpreted with caution given our study was underpowered to detect modest differences. Our findings provide increased support for BLC's clinical role in reducing bladder cancer recurrence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Practice Points

- Blue Light Cystoscopy (BLC) has become an important clinical procedure for bladder cancer management. Recent 2021 meta-analysis of 8 randomized control trials showed that BLC significantly reduced recurrence rate at 12 months compared to white light alone (risk ratio 0.70, 95% CI, 0.51–0.95). And further, WLC can fail to detect cases of NMIBC as compared to BLC, with those tumors that remain unidentified potentially able to progress to a higher stage and lead to more aggressive interventions, including chemotherapy and need for cystectomy. However, there is currently a lack of real-world data evaluating the risk of bladder cancer recurrence and progression in an equal access setting, and by race, among those treated with BLC.
- Herein, we report real-world bladder cancer outcomes following BLC utilization in the largest equal-access setting in the United States, the Veterans Health Administration. In our cohort of 378 patients with non-muscle invasive bladder cancer (NMIBC), we found that BLC was significantly associated with a 30% reduction in bladder cancer recurrence (HR 0.70; 95% CI, 0.54–0.90). Further, there were no significant difference in recurrence, progression, and overall survival following BLC by Black vs. White race.
- Mitigating recurrence is an unmet need for NIMBC patients, as upwards of 60% of these patients have recurrent bladder cancer within 1 year. Our data lends continued evidence that BLC may be better than WLC in reducing bladder cancer recurrence risk, which supports current AUA/SUO guidelines recommending BLC usage in patients with NMIBC to increase detection and decrease recurrence.

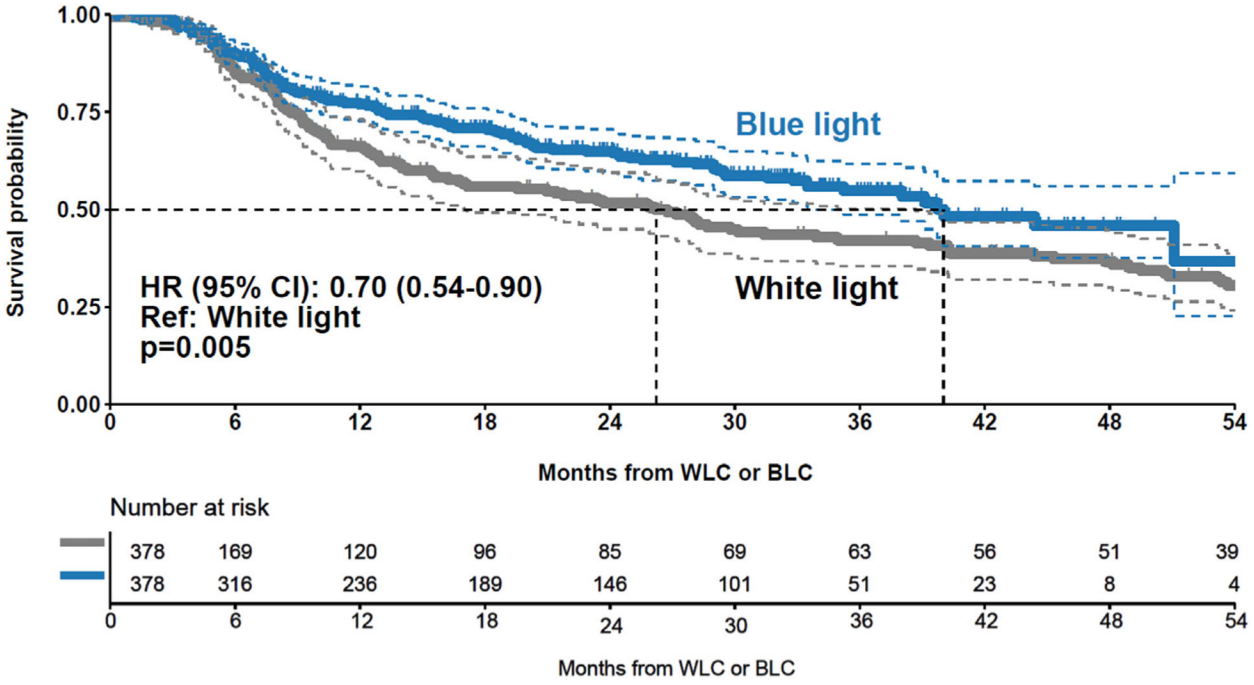

Fig. 1.

Kaplan-Meier curves of blue light vs. white light recurrence.

Table 1

Patient Demographics and Clinical Characteristics.

Characteristic	Patient Data (N = 378) N (%)
Age at diagnosis, Median (IQR), years	71 (65, 75)
Sex, n (%)	
Male	373 (99)
Female	5 (1)
Race, n (%)	
White	300 (79)
Black	43 (11)
Asian or Pacific Islander	12 (3)
American Indian or Alaska Native	4 (1)
Unknown	19 (5)
Ethnicity, n (%)	
Not Hispanic or Latino	347 (92)
Hispanic or Latino	19 (5.0)
Unknown	12 (3)
Bladder cancer diagnosed at a VA center, n (%)	
Yes	351 (93)
No	27 (7)
Smoking status, n (%)	
Former	197 (52)
Current	97 (26)
Never	84 (22)
Progression type, n (%)	
NMIBC to MIBC progression	13 (3)
N Stage progression	4 (1)
M Stage progression	5 (1)
Progression by cystectomy	11 (3)
Progression by radiation therapy	4 (1)

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Characteristic	Patient Data (N = 378) N (%)
Progression by systemic chemotherapy	2 (1)
No progression	339 (90)
Clinical grade group, n (%)	
TaLG only	127 (34)
Cis with or without TaHG or T1	52 (14)
TaHG or T1 without Cis	194 (51)
Cystectomy received, n (%)	
Yes	12 (3)
No	366 (97)
Type of chemotherapy regimen, n (%)	
Systemic	5 (1)
Intravesical	180 (48)
No chemotherapy	193 (51)
BCG treatment received, n (%)	
Yes	239 (63)
No	139 (37)

Table 2

Recurrence Type and Kaplan-Meier Estimated Median Time to Recurrence and Time-Point Recurrence-Free Rates.

	Overall Recurrence[1]*	WL Recurrence[2]	BL Recurrence[3]
Events/N	227/378	147/378	136/378
Median (95% CI) (month)	30 (26–40)	26 (17–39)	40 (33 NE)
12 months Est (95%) CI)	71% (66–76)	66% (60–73)	77% (73–82)
24 months Est (95%) CI)	56% (51–62)	52% (45–59)	65% (60–71)
36 months Est (95%) CI)	47% (42–53)	42% (35–50)	55% (49–62)
48 months Est (95%) CI)	41% (36–48)	37% (30–45)	46% (38–56)
60 months Est (95%) CI)	32% (26–39)	27% (21–35)	37% (23–59)

[1]Overall recurrence was defined as the first recurrence after diagnosis. The index date was the date of bladder cancer diagnosis. Patients who did not recur by the most recent follow-up date were censored.

[2]WL recurrence was defined as the first recurrence after WLC but prior to BLC. The index date was the date of diagnosis. Patients who did not recur prior to BLC were censored.

[3]BL recurrence was defined as the first recurrence after BL. The index date was the date of BLC. Patients who did not recur after BLC until the most recent follow-up date were censored.