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# The Impact of Blue Light Cystoscopy on the Diagnosis and Treatment of Bladder Cancer

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**Abstract** Photodynamic diagnostic technique with blue light cystoscopy (BLC) takes advantage of the preferential uptake and accumulation of protoporphyrins in neoplastic tissue which emit a red fluorescence when illuminated with blue light (360–450 nm wavelengths). This allows enhanced visualization of small papillary tumors and flat carcinoma in situ lesions that might have been missed on white light cystoscopy (WLC). There is compelling evidence that the ability of BLC to detect these additional tumors translates into improved recurrence rates compared to WLC. However, the impact of BLC with regard to progression rates and in patients who are managed with intravesical therapy is not yet known. Further work is required to optimize the integration of BLC into clinical practice, but the future for BLC appears promising.

**Keywords** Blue light cystoscopy · Cysview · Hexaminolevulinate · Non-muscle invasive bladder cancer (NMIBC) · Photodynamic diagnostics · Transurethral resection of bladder tumor (TURBT)

## Introduction

Transurethral resection of bladder tumor (TURBT) is one of the most common procedures performed by urologists, yet it is an underappreciated skill. Many overestimate their performance of what is often believed to be a simple operation [1•]. The overall rate of low-quality TURBT can be identified in studies looking at the rates of residual disease and understaging found on restaging TURBT, and the high rate of disease identified after intravesical therapy in those who had not received a restaging TURBT [1•]. Many argue that short-term recurrences often reflect missed or incompletely treated tumors [2], with as many as 70% of patients with non-muscle invasive bladder cancer (NMIBC) experiencing tumor recurrence within 5 years [1•]. The standard of care for TURBT remains white light cystoscopy (WLC), yet there is concern over the ability of WLC to identify small papillary tumors and flat carcinoma in situ (CIS) lesions. Thus, improvements in identifying disease missed on WLC may result in reduced recurrences, increased effectiveness of BCG, and improved patient counseling on early radical cystectomy.

Blue light cystoscopy (BLC) has emerged as an adjunctive modality to WLC that could improve the identification of missed lesions, thus improving TURBT quality with the promise of a more complete resection. In this review, we will focus on the latest evidence regarding BLC.

## How BLC Works

BLC, sometimes also referred to as fluorescence-based photodynamic diagnostic technique, takes advantage of the preferential uptake and accumulation of protoporphyrins in neoplastic tissue [3, 4]. These protoporphyrins then undergo conversion to photoactive porphyrins that emit a red fluorescence when illuminated with blue light (360–450 nm wavelengths) [3, 4]. This allows enhanced visualization of neoplastic lesions that might have been missed on WLC.

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Two protoporphyrin analogues, 5-aminolevulinic acid (5-ALA) and its more potent ester derivative hexaminolevulinate, have been investigated clinically. While there have been several clinical studies using 5-ALA, this agent is not approved by either the Food and Drug Administration (FDA) or European Medicines Agency (EMA) [5]. On the other hand, hexaminolevulinate (marketed as Hexvix/Cysview by Photocure, Norway) has been approved in Europe and in the USA for "as an adjunct to white light cystoscopy in the detection of non-muscular invasive papillary cancer of the bladder in patients with known or suspected bladder cancer." There is further evidence to suggest that hexaminolevulinate is superior to 5-ALA with regard to greater tissue penetration, higher fluorescence, and better ease of use [6, 7]. For these reasons, this review will focus on primarily on hexaminolevulinate-based BLC.

## Impact on Tumor Detection

Multiple studies and subsequent meta-analyses have shown that BLC significantly increases the rate of detecting small Ta lesions and CIS that were missed by WLC [3, 4, 8, 9]. Furthermore, use of BLC also reduces residual tumor rates by nearly threefold compared to WLC alone [10, 11].

The precise effect of BLC on tumor detection rates is difficult to calculate due to some studies reporting tumor detection at the patient level, while others report at the lesion level. With regard to papillary tumors, meta-analyses estimate an approximately 10–15% increased rate of identifying small papillary Ta tumors with BLC [3, 8, 9]. Individual studies have reported rates as high as 30–42% for BLC to improve the ability to detect papillary lesions [3, 12]. Detecting additional small papillary tumors with BLC is likely to be most beneficial in healthcare systems where you cannot simply fulgurate small tumors in the office. While BLC cannot distinguish between high-grade and low-grade bladder cancer, many urologist are skilled enough to make this distinction on WLC [13]. An important caveat to the increased papillary tumor detection with BLC is it rarely increases the detection of residual T1 tumors [3], which limits its impact on reducing under-staging.

On the other hand, BLC ability to detect occult CIS is potentially very impactful. BLC has repeatedly demonstrated an increased rate of nearly 40% for detecting flat appearing CIS compared to WLC ($p < 0.001$) [9, 14, 15]. One may argue that the identification of additional CIS lesions in some high-risk NMIBC patients is unlikely to change management since most are likely to already receive adjuvant BCG. However, in 25% of cases where BLC was able to detect CIS, WLC had only shown visibly normal mucosa [9•]. This is promising for the challenging clinical scenario of the positive urinary cytology in the setting of visibly normal WLC. BLC could potentially change management for these patients [16]. Yet, WLC cannot be omitted because 15% of CIS missed by BLC is reportedly only seen with WLC [14], emphasizing that BLC is adjuvant, not replacement, to WLC.

## Impact on Tumor Recurrences

The improved tumor detection rate from BLC appears to translate to a comparative improvement in short-term and long-term recurrence rates, with most trials demonstrating statistically significant improvements over WLC [8, 15, 17, 18].

Recurrence rates are estimated to be improved with BLC compared to WLC by as much as 8, 12, and 17% at 3, 6, and 12 months, respectively [3]. One meta-analysis of pooled data from 1345 patients reported a 12-month recurrence rate of 34.5% for BLC versus 45.4% for WLC ($p < 0.01$; RR 0.76 [0.63–0.92]) [9•]. In another meta-analysis of 12 randomized trials involving 2258 patients, BLC had improved recurrence-free survival at 1 year (HR 0.69; $p < 0.001$) and at 2 years (HR 0.65; $p < 0.001$) [19]. The median time to first recurrence was 9.4 months for WLC and 16.4 months for BLC ($p = 0.04$) in one prospectively randomized trial [20].

## Impact on Disease Progression

While the evidence demonstrating a recurrence benefit for BLC is relatively robust, the impact of BLC on progression has been mixed [2, 21]. This is due in part to the inconsistent progression definitions used between trials. Additionally, no trial to date has been designed to adequately power to detect a difference in progression.

Despite these limitations, there is some suggestion of a potential improved progression benefit with BLC. For example, in a randomized phase III trial with 4.5 years median follow-up using the progression definition of development of muscle invasive disease, a non-statistical significant improvement in progression rate was found for BLC (3.1% [8/255] for BLC vs. 6.1% [16/261] for WLC, $p = 0.07$) [20]. When the International Bladder Cancer Group (IBCG) re-analyzed the results of that same trial using their own IBCG progression definition that includes an increase in stage and/or grade, they found a progression rate of 17.6% (46/261) for WLC and 12.2% (31/255) for BLC ($p = 0.06$). This included progression from Ta to CIS in 4.2% of WLC patients and 1.6% of BLC patients. Using the IBCG progression definition, BLC was associated with an improved progression free survival ($p = 0.05$) [22].

Further evidence of a progression benefit comes from a recent meta-analysis of 4 randomized trials and 1 retrospective study between 2000 and 2016 [23]. Progression as defined by the included study occurred in 70 of 657 WLC patients (10.7%) and in 44 of 644 BLC patients (6.8%) (odds ratio 1.64, 1.10–

2.45; $p = 0.01$) [23]. The median follow-up was 28.9 and 27.6 months for WLC and BLC patients, respectively. This meta-analysis was substantially limited by not having a uniform definition of progression.

But before the actual impact of BLC on progression can be determined, prospective randomized trials designed with progression as their primary endpoints will be required.

## Challenges of Implementation and Unanswered Questions

A potential barrier for BLC is concerns that results may be heavily operator dependent. In a prospective, observational study of eight Spanish centers found that BLC sensitivity for lesion detection with BLC varied dramatically across centers, ranging from 84.2 to 98.2% and the false positive rate varied from 6.1% to a remarkable 39.3% [24•]. This raises concerns over the learning curve for BLC which may limit the ability of BLC to improve outcomes at lower volume centers, who already have demonstrably worse outcomes with WLC compared to high volume centers [1•]. The authors of the multicenter Spanish study suggested that five cases were not enough experience, and at least 10 cases would be required [24•]. However, the learning curve for BLC may be as many as 20–30 cases before proficiency is acquired [25]. Greater experience with BLC will likely improve detection rates and decrease the rate of false positives, as the surgeon becomes more comfortable interpreting potential false positive fluorescence from inflammatory lesions from prior biopsy sites or recent intravesical treatment. Occasionally increased fluorescence may also be seen along the trigone due to the angulation that could result in a false positive biopsy. Making a deliberate effort to correlate clinical observations with pathologic results will likely speed up the learning curve with BLC.

There is also concern that the observed benefits in tumor detection seen with BLC may be exaggerated due to methodological flaws in trials that BLC patients received more complete cystoscopic evaluations independent of photodynamic diagnostics. This is best demonstrated in an analysis looking at three trials that reduced the chance of performance bias by either blinding or randomizing to BLC only after WLC was completed. When performance bias was reduced, no benefit from BLC was seen [2]. Some argue that several of the lesions identified on BLC might have been identified had a more careful and through WLC been performed. However, these claims are difficult to prove.

It is also unclear how intravesical therapy might reduce some of the demonstrated benefits of BLC. The findings of one prospective randomized trial suggest that the utilization of adjuvant therapy such as single dose perioperative mitomycin may mitigate the recurrence-free survival benefits of BLC [26•]. Yet, other series still find a benefit in reducing recurrences with BLC even when intravesical chemotherapy is given for intermediate-risk patients and BCG is given for high-risk cases is given [15].

Some of the other obstacles facing BLC are practical, beginning with the need for preoperative intravesical administration of the hexaminolevulinate contrast agent typically for an hour. An upfront investment for a blue light source, specialized lens, and camera head is also required. In the USA, the FDA approval for hexaminolevulinate is linked to the Karl Storz rigid scope, but this is not the case with the European approval. Several studies suggest that the benefits of reduced recurrences with BLC can offset the increased associated costs, at least at high volume centers [18, 27, 28]. At lower volume centers, BLC might be prohibitively expensive investment. This again raises concerns about BLC improving outcomes at low volume centers who might be underperforming with WLC.

Another practical concern in the USA is that the FDA approval is currently for one instillation of hexaminolevulinate only. This is due to concerns over potential reactions from multiple instillations. These concerns now appear to be unfounded as even multiple instillations of hexaminolevulinate appear safe [29, 30]. In Europe, the EMA approval allows for unlimited instillations. Multiple instillations would be beneficial for the expansion of BLC to office based flexible blue light cystoscopy [31], which is currently being investigated (NCT02560584). However, while BLC will likely be helpful in identifying some recurrences, hexaminolevulinate is not approved for patients who received intravesical immunotherapy or chemotherapy within 90 days due to the high false positive rates from inflammation. This especially limits the value of BLC for patients receiving maintenance intravesical therapy and it is unknown how BLC could be optimally integrated into managing these patients. It is also unclear how BLC improved detection for occult CIS will effect trials involving the recently defined BCG "unresponsive" disease population [32].

## Conclusions

There is compelling evidence that BLC enhances the ability to detect additional small papillary Ta tumors and CIS that were missed on WLC, resulting in improved recurrences rates. Guidelines from the European Urology Association and the International Consultation on Urological Disease support the use of BLC, and more recently the AUA/SUO NMIBC guidelines also recommend enhanced cystoscopy, such as BLC (Moderate Recommendation; Evidence Strength: Grade B) [33•]. However, the impact of BLC with regard to progression rates and in patients who are managed with intravesical therapy is still unknown. Further work is required to optimize the integration of BLC into clinical practice, but the future for BLC appears promising.

**Compliance with Ethical Standards**

**Conflict of Interest** Eugene J. Pietzak declares no potential conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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