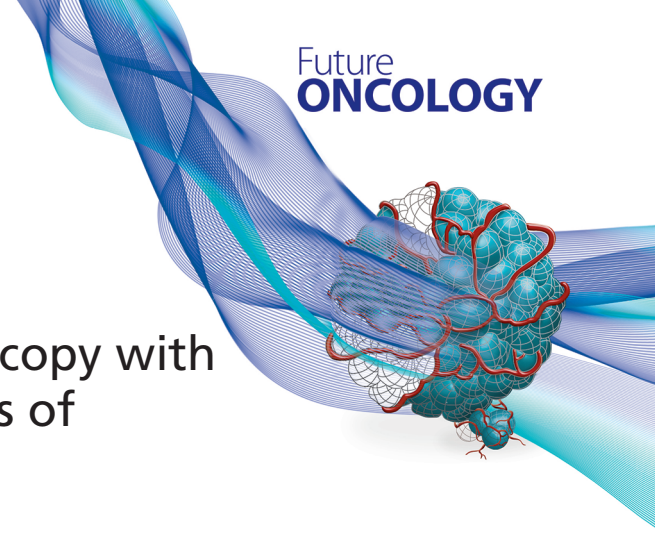
Device Evaluation

Future ONCOLOGY



The use of blue light flexible cystoscopy with hexaminolevulinate & the diagnosis of bladder cancer

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Blue light cystoscopy improves the detection of bladder cancer at time of transurethral resection of bladder tumor for nonmuscle-invasive bladder cancer. This has translated to decreased tumor recurrence. Given this improvement in rigid cystoscopy, the question remains whether the use of blue light flexible cystoscopy (BLFC) in the surveillance setting provides the same benefits. This review aims to evaluate the recently reported Phase III prospective multicenter study of BLFC which evaluated the detection of bladder cancer during surveillance, which in its earliest reporting demonstrated improved detection of bladder cancer. This study evaluated 304 patients with findings of 63 confirmed malignancies, with 13 (20.6%) only identified by BLFC ($p < 0.0001$). The question still remains whether the improved detection rate will translate to improved clinical outcomes. Further, studies will be necessary to determine which patients will benefit from BLFC, optimal ways to incorporate into surveillance strategies and cost–effectiveness.

First draft submitted: 24 April 2018; Accepted for publication: 22 May 2018; Published online: 21 June 2018

Keywords: blue light flexible cystoscopy • nonmuscle-invasive bladder cancer • white light cystoscopy

Nonmuscle-invasive bladder cancer (NMIBC) is a predominant diagnosis for those newly diagnosed with bladder cancer [1]. These noninvasive tumors have a high recurrence rate: 50–70% and 10–20% will progress to muscle-invasive disease [1]. Management of NMIBC with transurethral resection of bladder tumor with use of BCG or intravesical chemotherapy decreases the risk of recurrence and progression [2,3]. Surveillance protocols for NMIBC patients involve frequent monitoring with cystoscopic evaluation in the outpatient setting. White-light cystoscopy (WLC) has long been the standard for cystoscopic surveillance evaluation with a high sensitivity of detecting papillary lesions. Unfortunately, WLC is limited in detection of flat lesions with false-negative rates over 10% overall and 20% for carcinoma *in situ* [4,5].

Since then, many early recurrences represent missed tumors or inadequate initial resection due to suboptimal visualization [6], but enhanced cystoscopic methods have now been developed to improve the visual detection of bladder cancer. WLC remains the standard for detection of bladder cancer, but enhanced cystoscopy with blue light frequently detects tumors that are missed by white light. In fact, the AUA guidelines for managing NMIBC state that "in a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of transurethral resection of bladder tumour (TURBT), if available, to increase detection and decrease recurrence (moderate recommendation; Grade B)" [2].

Outpatient white light flexible cystoscopy (WLFC) is a gold standard procedure used to detect and follow patients with bladder tumors [2]. Given the likelihood of missed tumors in the critical surveillance setting and the evidence of improved detection with blue-light cystoscopy (BLC) in the operative setting, there is a clear role for using blue light flexible cystoscopy (BLFC) to improve surveillance. A recent prospective Phase III clinical study in USA has evaluated the use of BLFC in office surveillance. The goal of this article is to review the current evidence regarding BLFC for bladder cancer surveillance.

Future Medicine

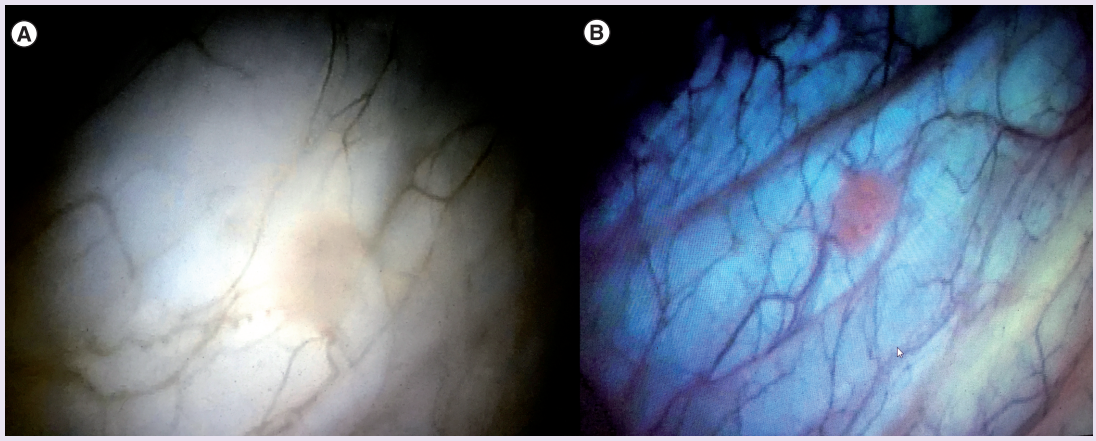

Figure 1. Papillary bladder tumor. Visualized with white light flexible cystoscopy **(A)** and blue light flexible cystoscopy **(B)**.

Blue light technology

BLC is not a new procedure and has seen recent increased use in the operative setting as a US FDA approved photodynamic diagnostic technique [7]. BLC is an adjunct to WLC to allow for improved visualization of bladder cancer. The procedure involves intravesical instillation of a photoactive porphyrin, such as hexaminolevulinate (HAL), which preferentially accumulates in neoplastic tissue, where it induces an accumulation of protoporphyrin, which fluoresces red when exposed to blue light (Figure 1) [7,8]. This enhancement improves the demarcation between normal and neoplastic tissue, which allows for improved detection of not only exophytic tumors but flat tumors as well.

While BLC has been utilized at time of TURBT with rigid cystoscopy, it can also be applied to the outpatient office setting with flexible cystoscopy. The current BLFC platform is the D-Light C PDD flexible videoscope system (Karl Storz Endoscopy-America Inc., CA, USA) that contains a chip on the tip to be utilized with HAL [9,10]. The ability to improve detection of bladder tumors with the use of BLFC was demonstrated as early as 2005 [10,11]. These early studies did randomize patients to the use of BLFC versus WLFC but when combined included less than 70 patients. Combined analysis demonstrated improvement in detection with WLFC versus BLFC of carcinoma in situ (CIS; 61 vs 77%), pTa (86 vs 91%) and pT1-2 (81 vs 91%) [12]. Given the limited evidence, the European Association of Urology has yet to recommend the standard use of BLFC [12]. While these early studies served to demonstrate the feasibility and safety of BLFC, this has only recently been brought to the USA and recently completed its prospective multicenter Phase III clinical trial [9].

Blue light cystoscopy

BLC is routinely performed in the operating room and multiple Phase III studies have demonstrated improved detection of tumors at time of TURBT. Prospective studies and meta-analysis utilizing raw data of NMIBC patients comparing BLC with WLC demonstrate significantly improved detection rates with BLC especially of CIS, Ta and high-grade tumors [13–17]. With this improvement in tumor detection long-term follow-up has translated to decreased recurrence rates and delayed time to recurrence [13,16,18,19]. There is still insufficient data regarding impact on progression but there is reason to expect that earlier detection of patients with BCG-unresponsive disease, for example, with consequent change in management may translate into improved progression and survival benefit [20].

Phase III study of BLFC

This was a prospective, open-label, comparative, within patient and controlled Phase III study performed at 17 centers in the USA [9]. Those who were eligible required a history of multiple, recurrent or high-grade bladder tumors. Patients were excluded if they had received BCG immunotherapy or intravesical chemotherapy in the prior 6 weeks. This cut-off was utilized to reflect clinical practice as surveillance cystoscopy is often performed 6 weeks after last instillation.

At each patient's first office-based surveillance visit, all patients had a cytology obtained (although not utilized in decision making) and then underwent an instillation of HAL. Patients then underwent flexible cystoscopy in an office setting under local intraurethral anesthesia. Initial evaluation was with WLFC with documentation of number, size and appearance of all suspected malignant lesions. Following WLFC, patients were randomized to undergo either BLFC or not and suspicious lesions were again recorded. The randomization was included to make sure the initial WLFC was performed optimally, since the urologist would not know, if a BLFC would be performed. Patients with suspicious findings under either method were referred to the operating room and underwent evaluation and resection according to normal clinical practice under both white and blue light with specimens separated according to method used. A consensus panel of pathologists were blinded to the method and determined final pathology.

The primary efficacy end point was the proportion of patients with histologically confirmed malignancy that was detected only by BLFC and not by WLFC in the surveillance setting. Secondary efficacy end points centered around the operative resection which included the proportion of patients with CIS lesions or additional tumors identified with BLC but not seen with WLC. The primary safety end point was the proportion of patients with adverse events following surveillance.

Efficacy

The study enrolled 304 patients including 202 with prior high-grade tumors. The tumor stage at prior TURBT was CIS in 100 (33%) and T1 in 52 (17%). There were 184 (61%) with 1–4 prior recurrent tumors for a mean of 1.7 ± 2.03 prior recurrences. Intravesical therapy with BCG or chemotherapy within 90 days was present in 202 patients (66%). In total, 103 patients were taken to the operating room due to a suspicious lesion being identified, out of which 63 (41%) had confirmed bladder cancer. In evaluation of the primary efficacy end point, 13 patients (20.6%; 95% CI: 11.5–32.7) had malignant recurrences only detected with BLFC ($p < 0.0001$) and five of these were confirmed as CIS. WLFC detected only one malignant recurrence that was not seen with BLFC. There was a 9.1% false-positive rate in both the WLC and BLFC arms. This is consistent and better than prior BLC meta-analysis [17] and highlights that although the majority of patients had undergone either intravesical immunotherapy or chemotherapy within 6 weeks to 90 days, the inflammation did not result in a higher false-positive rate. It should be noted that only six of 63 patients with recurrent tumors had a positive urine cytology and 13 had suspicious cytology. With 26 CIS lesions identified and only six positive urine cytology, this highlights the need for enhanced cystoscopy, since relying on cytology to detect CIS missed by white light cystoscopy is likely inadequate to find most cancers.

As a secondary analysis, an evaluation of BLC in the operative setting was performed in 103 patients with identification of 63 pathologically confirmed bladder tumors. Of those patients with malignancy identified, 26 had CIS, of which nine (35%; 95% CI: 17.2–55.7, $p < 0.0001$) were found with BLC alone. This is consistent with analysis of multiple Phase III studies with detection of CIS by BLC alone, which identifies 20–40% of CIS tumors resulting in a significant detection rate of 0.87 versus 0.75 for WLC ($p = 0.006$) [14,21]. In the current study, BLC also detected malignant lesions missed with WLC in 29 of the 63 patients (46%; 95% CI: 33.4–59.1). 23% of these patients identified one or more Ta or T1 tumors not detected by WLC, which is consistent with prior Phase III studies [15,16]. At this time, there is no follow-up available for analysis thus rates of recurrence or progression are unknown.

Safety

In this study, only 12 adverse events were seen in 11 patients [9]. The adverse events thought to be related to the procedure itself included dysuria, urethral pain, bladder discomfort, erythema and pruritus but none resulted in serious injury. This is similar to Phase III studies using HAL in the operating room with 2.4% of the patients experiencing a minor adverse event related to the procedure [15].

Patient-reported outcomes

A second evaluation of the Phase III BLFC study involved the analysis of patient-reported outcomes which is currently in submission [22]. Due to the need for an additional catheterization with instillation of HAL and subsequent waiting period, the pain and anxiety associated with the procedure was evaluated. At three separate time points, the patients were asked about pain and anxiety: the screening visit, following surveillance cystoscopy and for those referred to the operating room, after pathologic diagnosis. Anxiety related to the diagnosis was measured

using the Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety 4a form and pain was measured using the PROMIS Pain Intensity 1a form which ranked pain on a scale from 0 (no pain) to 10 (worst pain) [23]. Following each procedure, the patients were evaluated as to their willingness to pay using the 'Was it Worth It (WIWI)'? questionnaire.

In an evaluation of anxiety, there was a decrease in anxiety based on the PROMIS anxiety score after surveillance BLFC with the greatest decrease in those with a negative BLFC ($p = 0.051$). Although not statistically different, the authors note that the point decrease is considered meaningful for those who utilize the anxiety survey. This would provide further reassurance with a negative fluorescence cystoscopy than those who only underwent WLFC. There was also a decrease in those following operative evaluation, but this was driven by the lower anxiety scores of those with negative pathology on biopsy. The only increase in anxiety noted were in those patients with intermediate risk disease who subsequently had a positive BLFC.

The evaluation of pain uniquely found continuously low-pain scores even postsurveillance cystoscopy and postoperative interventions. This demonstrates that the instillation and catheterization were of minimal to no bother to the patients in this study. The majority of patients noted either improved or stable quality of life overall when compared with their baseline before the BLFC. Over 90% of patients who underwent BLFC experience felt it was worthwhile and would recommend to others.

With regards to patients' willingness to pay out-of-pocket for BLFC, the majority were willing to pay US$100 or more. 60% of those postsurveillance cystoscopies and 56% postoperative procedure were willing to pay ≥US$100. Less than 30% in both settings were unwilling to pay out-of-pocket for BLFC. This willingness to pay survey contributes to the notion of perceived benefit to the patients undergoing the study. It is maybe not unusual that the patients have a general positive perception of enhanced photodynamic diagnostic techniques as patients tend to have more faith in a cystoscopic evaluation than other tests such as urinary markers [24].

Conclusion

Clinical utility

Long-term follow-up of the Phase III study will ultimately determine the clinical utility of BLFC. While the above analysis has demonstrated improved detection of malignant tumors, especially CIS, the clinical efficacy will ultimately require demonstration of decreased and delayed recurrence and possible decreased progression of bladder cancer. While this is seemingly easy to follow after operative TURBT, it will be more difficult to demonstrate in the office surveillance setting as the treatment paradigm can differ following identification of suspected bladder tumors.

As the clinical utility of BLFC continues to undergo evaluation, studies will also need to evaluate the roles of intravesical chemotherapy and office fulguration in the treatment paradigm. Studies have already compared postoperative instillation of mitomycin C with BLC in an analysis of recurrence rates with similar results [25]. Given the multiple treatments and management strategies for NMIBC, there will ultimately need to be a risk stratification to determine which patients are to benefit the most from BLFC. There is currently a registry to collect data on BLC in the operating room and expansion to include surveillance patients will be valuable to assess long-term benefits.

Cost–effectiveness

Bladder cancer has been designated as the most expensive cancer from diagnosis to death in the USA per capita largely due to the lifetime surveillance of those patients with NMIBC [26,27]. From the time of initial diagnosis, bladder cancer patients are essentially committed to years of invasive procedures to monitor for recurrent disease based on guideline recommendations [2,3]. The invasive nature of surveillance likely contributes to the poor adherence to guidelines by both patients and practitioners [28,29]. Unfortunately, these recommendations for surveillance strategies have a paucity of studies and rely on observational data or expert opinions and thus have led to more intensive and conservative protocols [2,3]. This is clearly where BLFC will need to prove its efficacy by being able to decrease the number of future procedures for NMIBC patients and ultimately demonstrating the cost savings. This has been demonstrated with BLC, which will likely lead to wider acceptance of its use [30]. Of course, this is always limited, given differences in various healthcare systems and the upfront expense for the BLC platform.

Practical considerations

The incorporation of BLFC requires several considerations. There is capital equipment that needs to be acquired to perform the procedure in the outpatient setting including ordering of Cysview (Photocure Inc., NJ, USA). Patients

need to be identified for the procedure prior to clinic visit so they can arrive 1 h prior to the procedure to have instillation of Cysview. This requires determination of which patients should undergo BLFC. Early consideration from the prospective randomized trial is that intermediate and high risk patients could benefit especially early in their surveillance course when risk of recurrence is highest. Likely low-grade patients with large tumors or at their initial 3-month surveillance may also benefit. Furthermore, patients with abnormal lesions that are not classic for bladder cancer may benefit from returning to clinic for BLFC to determine, if lesions merit an operation.

Executive summary

Blue light flexible cystoscopy identifies significantly more bladder tumors than white light flexible cystoscopy

- Phase III, prospective, multi-center study found 13 patients (20.6%; 95% CI: 11.5–32.7) with malignant recurrences only detected with blue light flexible cystoscopy (BLFC; $p < 0.0001$).

BLFC increases ability to identify CIS

- In the Phase III trial, five patients with CIS were identified on BLFC only of the 26 total CIS lesions identified in the study.

BLFC has minimal toxicity

- Of 304 patients, only 12 minor adverse events including urethral pain, dysuria and bladder discomfort.

Patient-reported outcomes

- There is a decrease in anxiety after surveillance BLFC, with the greatest decrease in those with a negative BLFC ($p = 0.051$).
- Despite need for instillation of hexaminolevulinate with catheterization there are very low pain scores.
- Over 90% of patients who underwent BLFC experience felt it was worthwhile and would recommend to others.

Conclusion

- BLFC is a safe and effective procedure in the outpatient surveillance setting to allow for increased detection rate of malignant bladder tumors.
- A prospective registry will provide additional data on future outcomes and cost–effectiveness.
- BLFC is an efficacious, safe and well-tolerated procedure for surveillance of nonmuscle-invasive bladder cancer

Financial & competing interests disclosure

Y Lotan is a consultant for Photocure and a participant in the Phase III BLFC trial. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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