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Photodynamic diagnosis of bladder cancer: Initial experience of a single UK centre

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Hexvix;
Blue light cystoscopy (BLC);
White light cystoscopy (WLC)

Abstract
Objectives: To describe the introduction and evaluate efficacy of photodynamic diagnosis with Hexvix for detecting tumours and abnormal mucosal lesions during transurethral resection of bladder tumour (TURBT).
Subjects and methods: Prospective study of consecutive eligible patients who underwent TURBT with aid of Hexvix-guided cystoscopy in a single District General Hospital (NHS Trust in England).
The participants selected were patients suspected to have bladder cancer or enlisted to undergo TURBT.
The main outcome measures were the number of tumours or abnormal mucosal lesions that were missed by white light cystoscopy (WLC) but detected by Hexvix, blue light cystoscopy (BLC).
Results: A total of 63 patients (39 males and 24 females; mean age 74 years; age range, 35–88 years) met study criteria. 15 were excluded: in 6 intra-vesical Hexvix was retained for <1 h, and in 4, TURBT was delayed by >1 h; of the remaining 53 patients, 5 were excluded for technical reason, failure of fluorescence. Seventy five lesions were detected in the remaining 48 patients. Of these, 51 (68%) were detected by WLC and BLC both. BLC detected additional 24 (32%) lesions that were missed by WLC. Of these lesions, 15 (20%) were cancer and 9 (12%) were inflammation or dysplasia.
Conclusion: BLC with Hexvix was easily introduced into a Bladder cancer management protocol and well tolerated by most patients. BLC increased diagnostic accuracy of cystoscopy during TURBT, although some of the lesions it detected were false positive.

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Introduction

Over 10,000 people are diagnosed annually with bladder cancer (BC) in the United Kingdom, where it is the 7th most common cancer [1]. Non-muscle-invasive BC (NMIBC) accounts for 75–85% of all newly diagnosed BC cases [2]. The 5-year survival rate of patients with bladder cancer confined to the mucosa (TaT1 NMIBC), is 80–90% [3]. About 25–75% will develop recurrent disease [3,4]. Many progress to muscle invasive BC (MIBC) or metastatic disease [5]. Of the TaT1 NMIBC recurrences, 25–60% may be due to incompleteness of TURBT because white light cystoscopy (WLC) does not visualize all tumour-bearing sites [6,7]. Indeed, check cystoscopies detect residual or recurrent disease in about 55% of cases [6–9].

The limitations of WLC led to the development of Photodynamic diagnosis, PDD with 5-Aminolevulinate (5-ALA) and Hexaminolevulinic acid (HAL; trade name Hexvix) respectively. It has been reported to improve recurrence-free survival (RFS) of patients with bladder cancer [7–18]. International expert panels have also produced guidelines for PDD with Hexvix, namely diagnosis of NMIBC that has not yet been subjected to TURBT, follow-up of patients with NMIBC, additional testing of patients with positive urine cytology but negative WLC, follow-up of patients with multifocal disease and suspected carcinoma *in situ* (CIS) [19,20]. A recent study by the Health Technology Assessment programme of the National Health Service of the United Kingdom came to three conclusions. First, PDD detects BC more sensitively but less specifically than WLC and is better at detecting more aggressive and higher risk tumours, including CIS. Second, compared to WLC, when PDD is used in the initial TURBT, fewer residual tumours are found by check cystoscopy and the RFS is longer. Third, it is not clear whether PDD at TURBT reduces tumour recurrence and progression in the long term better than WLC. Nevertheless, PDD provides additional benefits at a cost that society may be willing to pay [21]. The present study aimed to provide preliminary evidence to justify the routine use of Hexvix in our hospital and its introduction in all the Trust's hospitals.

Subjects and methods

PDD with Hexvix

Hexvix and 5-ALA are fluorochromes and haem precursors that are administered through a urethral catheter into the bladder to aid tumour detection on the basis of fluorescence [16,22,23]. They accumulate in tumour cells that metabolize them stepwise into first porphyrin and then protoporphyrin IX which generates a purplish fluorescence. This is detected as blue by D-light (Xenon lamp) by a specially developed light cable and special filter mounted on the cystoscope eye-piece which has dual blue and white light functions. This allows cystoscopic visualization of the tumours under white and blue light respectively (Fig. 1).

The chemical structure of Hexvix and 5-ALA are very similar: Hexvix is essentially 5-ALA plus a lipophilic hexyl moiety. However, Hexvix has four times the fluorescent power of 5-ALA. Hence, although 5-ALA was developed first and is available for oral and intravesical use, it is often replaced by Hexvix, which is currently only available for intravesical instillation. Hexvix is supplied as a powder that is dissolved in a 50 ml buffer solution before instillation into the bladder. The patient is expected to retain it within the bladder for at least 1 h prior to TURBT (by contrast, 5-ALA must be retained for 2–3 h before TURBT). Hexvix accumulates in cancerous bladder tissue and after illumination with blue light cystoscopy (BLC), a clearly visible purplish fluorescence is observed (Fig. 1a).

Hexvix was developed by Photo cure, ASA, Oslo, Norway and has been available, to UK Urologists, since about 2003.

Prospective trial

This prospective study of 63 consecutive patients with history of BC was performed between January 2009 and November 2010. The patients were included either because they had new presentation with bladder tumour, recurrent BC, positive urine cytology but a negative WLC or suspected CIS. Study approval was obtained from the Hospital Clinical Governance Committee. All patients consented to PDD with Hexvix.

Technique

Briefly, 85 mg of Hexvix was dissolved in 50 ml solvent and instilled into the bladder *via* a urethral catheter 1 h before TURBT. Patients

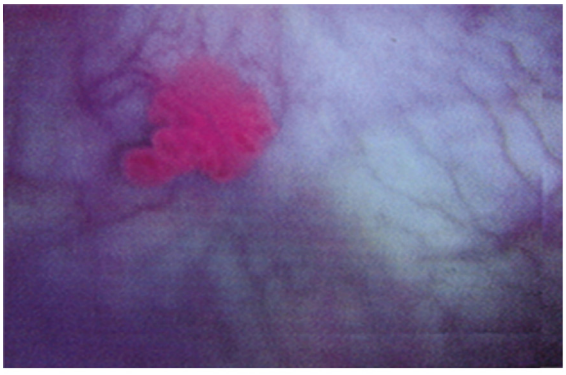


Figure 1 Blue light chemistry and tumour detection.

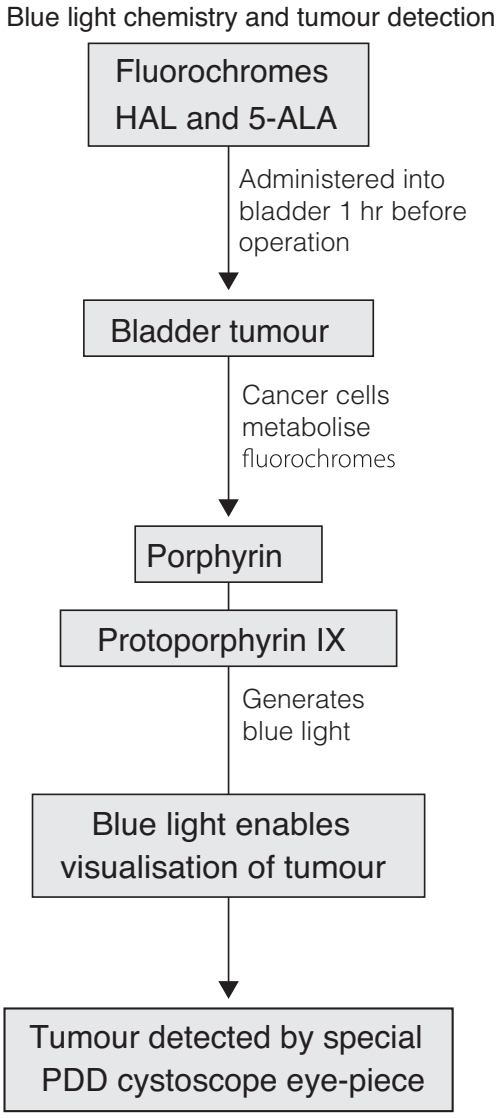


Figure 1 (*Continued.*)

who retained the intravesical Hexvix underwent cystoscopy with a Karl Storz PDD camera head with dual blue and white light functionality 60 min later. Those patients who were unable to retain intra-vesical Hexvix for 1 h and those who though retained Hexvix for 1 h, there was failure of fluorescence during cystoscopy were excluded from the study.

Endoscopically, the bladder mucosa was inspected in a stepwise fashion under WLC and BLC. A map of all tumours and abnormal areas seen were recorded separately and either resected or biopsied. The following steps were followed: First, during preliminary cystoscopy, presence of control fluorescence was noted in bladder neck. Second, fluorescence in the main tumour and elsewhere in the bladder was recorded. Third, all fluorescent areas outside the main tumour were biopsied using cold cup or loop as appropriate. Fourth, the main tumour was resected separately under WLC. Finally, to confirm complete resection of the main tumour and biopsy of all the abnormal-looking mucosa, BLC was performed. The locations from which the biopsies were obtained and the histology results including those recorded by BLC alone were recorded in the study protocol (Appendix).

Results

Sixty three patients (39 males and 24 females) age range 35–88 (mean 74) were recruited and consented to undergo Hexvix-guided cystoscopy (Fig. 2). Of these, 35 (55.6%) were new tumours, 20 (31.7%) recurrent tumour, 5 (7.5%) positive urine cytology without evidence of bladder tumour in conventional WLC and 3 (4.8%) suspected CiS (Table 1). Excluded were 6 patients who failed to retain Hexvix for 1 h, 4 (6.4%) where there was delay in cystoscopy beyond 1 h and 5 (7.9%) due to technical failure. The cystoscopy

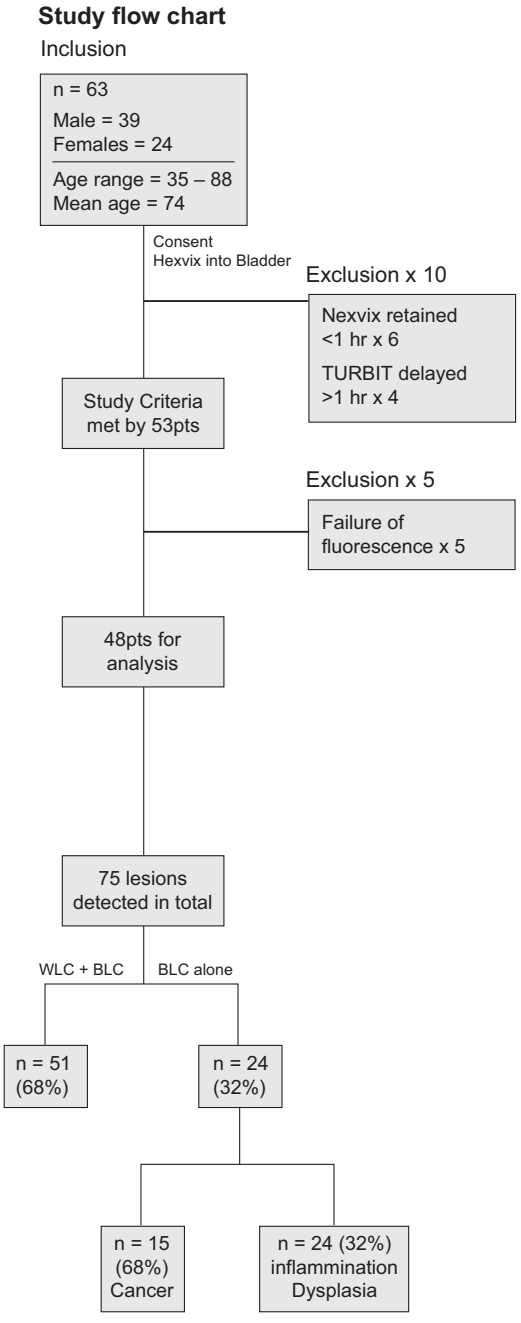


Figure 2 Study flow chart.

Table 1 Indications for blue light cystoscopy ($n = 63$) and reasons for exclusion ($n = 15$).

Indication for BLC	Number	Cases excluded failure to retain Hexvix	Delay in cystoscopy	Technical failure
New tumour	35 (55.6%)	5	1	1
Recurrent tumour	20 (31.7%)	1	3	4
Positive cytology but negative WLC	5 (7.9%)	–	–	–
Suspected CiS	3 (4.8%)	–	–	–
Total	63	6 (9.5%)	4 (6.4%)	5 (7.9%)

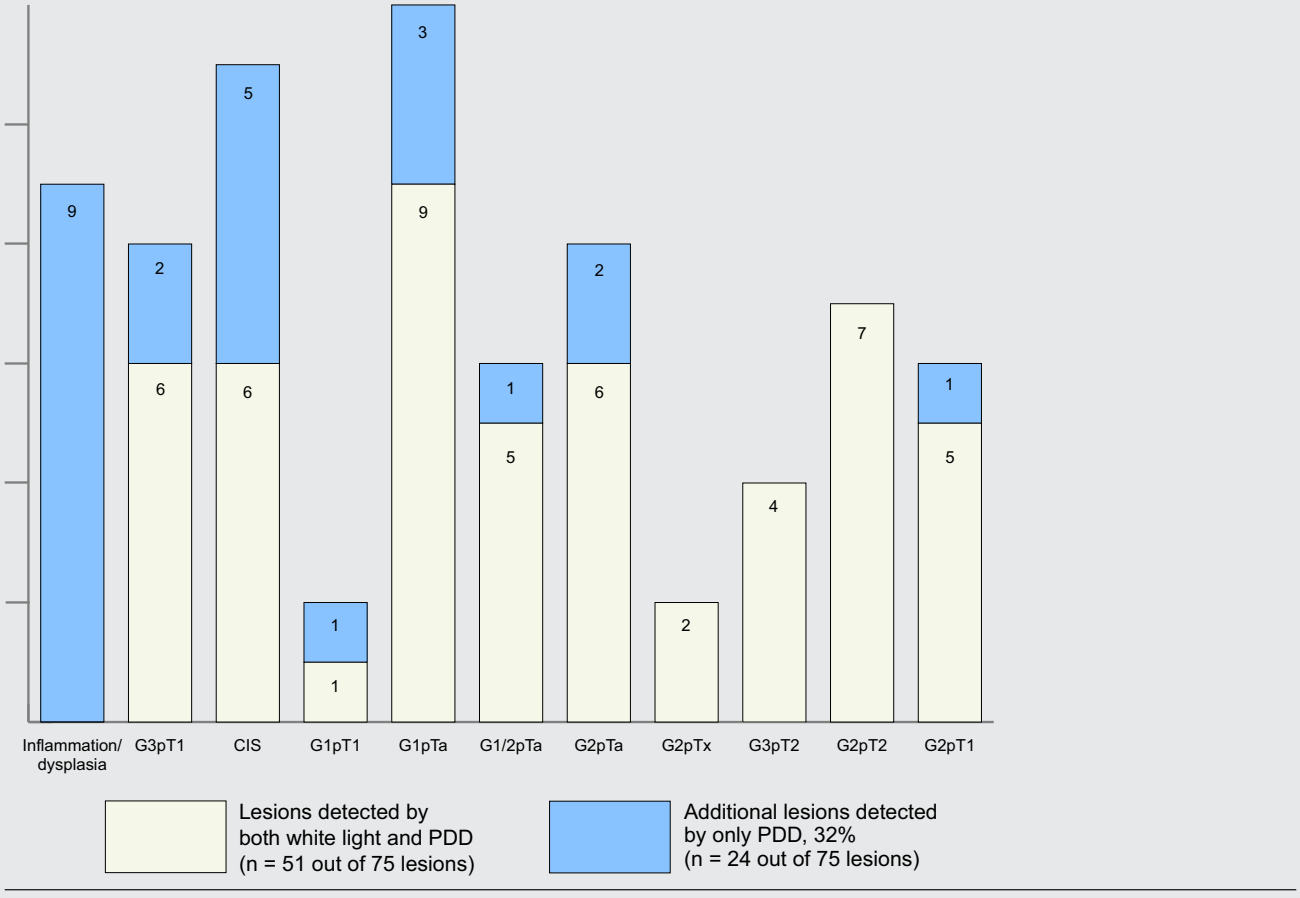
in the remainder 48 patients that fulfilled the criteria, resulted in detection of a total of 75 lesions of which 51 (68%) were visualized with both WLC and BLC. 24 (32%) lesions comprising 15 (20%) due to cancers and 9 (12%) inflammation were only obvious on BLC (Table 2). Thus, the addition of BLC led to the detection of extra lesions that were missed by WLC. These included high grade CiS and G3pT1 and false positive cases due to inflammation.

Discussion

In this study, the papillary tumours or lesions with a raised mucosa were usually detected by both WLC and BLC. However, 15 cases (20%) of all lesions detected in this study were flattish CiS and G1-3pTa-1 tumours which were only detected by using BLC. This is significant because the lesions may have been detected at a subsequent cystoscopy and probably misdiagnosed as a recurrence. Previous studies have also shown that 25–60% of BCs are not diagnosed at the time of TURBT [6–9]. Notably, 9 of the 24 lesions that were detected by BLC alone (12% of all 75 lesions) were due to inflammation. This relatively high frequency of inflammation detection with BLC alone (false positive) was probably a reflection of our learning curve.

The limitations of this study include the possibility of bias of the operating surgeon in favour of BLC. This can be eliminated by performing a randomized study where half of the patients are examined after WLC-guided resection by BLC and the other half are examined after BLC-guided resection by WLC.

Table 2 Histology of detected lesions.



Expert panels in the United Kingdom and Europe have recommended that BLC should be used routinely in all cases of initial TURBT, follow-up rigid cystoscopy (if Hexvix not used previously), positive urine cytology but negative WLC and follow-up of patients with multi-focal disease and CIS [19,21]. Our experience, feedback after presentations and discussions in our Trust wide multidisciplinary team meeting (Audit of Hexvix: Lessons learned and implications for clinical practise, October 2010. Unpublished) and during the British Association of Urological Surgeons North London Regional meeting (Audit of Hexvix: A district general hospital experience, December 2010. Unpublished), indicate that these expert recommendations are broadly accepted apart from the use of BLC in all new cases.

Thus whether BLC should be used in all initial TURBTs or only in selected cases remains controversial. There are two main objections to the use of BLC in all new cases. First, the risks of prolonged exposure to Hexvix or its use during pregnancy is not known [23]. Second, since large tumours are usually well visualized by WLC, and the aim of resection is often pathological staging, it is unclear whether TURBT of large tumours requires BLC at the initial resection. This is because many of these patients will ultimately require second look cystoscopy, at which point BLC can be performed. This selective approach, is not only associated with lower costs, it also allows associated superficial lesions to be identified, biopsied and/or resected during the mandatory precautionary second look. In any case, we have found that when a large papillary tumour is associated with multiple tiny satellite lesions, to ensure complete resection, it is useful to perform PDD at the initial TURBT to ensure complete resection.

We found that Hexvix is easily introduced into a BC management protocol after Hospital Clinical Governance Committee approval is obtained and the appropriate equipment (which should be compatible with existing endoscopic equipment) is purchased. As a result of our experience, the use of Hexvix has been introduced to the other Trust hospitals. Our study and others [7–18] show that Hexvix improves BC detection, and the other studies show that Hexvix improved RFS, and that society appears to be willing to pay for BLC [21]. However, it remains to be seen whether Hexvix will be universally adopted by Urologists and if so, whether it ultimately translates into reduced disease progression and improved long-term cancer survival (oncological outcome) that justifies the cost of intervention.

Conclusions

PDD with Hexvix is a valuable adjunct in the endoscopic management of BC. It is easy to introduce into a BC management protocol with a short learning curve for experienced Urologists. It is well tolerated by most patients and has been proved to increase the detection of tumours during TURBT, albeit with some false positive results.

The recommendation of Expert panels that PDD should be performed in all cases of initial TURBT is controversial. An alternative approach may be to recommend the routine use of Hexvix during the initial TURBT selectively based on the endoscopic characteristics of the tumour and patient history. However, it has a useful role in management of patients with positive urine cytology but negative WLC, multifocal disease and CIS.

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Ethical approval

The study was approved by the Clinical governance committee of the Hospital.

Author's contribution

The study was designed by Mr. Derek T.L. Turner. Mr. Samuel O. Osaghae drafted the manuscript. The draft was critically reviewed by Mr. Turner.

Competing interest

None.

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Appendix.

STUDY PROTOCOL

PILGRIM HOSPITAL HEXVIX AUDIT

Patient details or label

Date of procedure.....

Day case: .....

24 hour stay: .....

In-patient: .....

Minutes HexVix in bladder: .....

Indication	**Please tick those that apply**		
New tumour			
Recurrent tumour			
Positive cytology			
Target biopsy of CIS			
Cystoscopic Findings	**Please tick**		
Control fluorescence seen	Y	N	
Tumour seen	+ white light	+ fluorescence	
Tumour seen	+ white light	- fluorescence	
Mucosal abnormality	+ white light	+ fluorescence	
Mucosal abnormality	- white light	+ fluorescence	
Mucosal abnormality	+ white light	- fluorescence	
Mucosal normal			
Diagram:			
Histology	Please tick		
Tumour			
Muscle included			
Mucosal abnormality			
Difficulties/complications:			
Follow-up result	**Date**	**Follow-up result**	**Date**

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