EXPERT CONSENSUS DOCUMENT

Hexaminolevulinate blue-light cystoscopy in non-muscle-invasive bladder cancer: review of the clinical evidence and consensus statement on appropriate use in the USA

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Abstract | Hexaminolevulinate (HAL) is a tumour photosensitizer that is used in combination with blue-light cystoscopy (BLC) as an adjunct to white-light cystoscopy (WLC) in the diagnosis and management of non-muscle-invasive bladder cancer (NMIBC). Since being licensed in Europe in 2005, HAL has been used in >200,000 procedures, with consistent evidence that it improves detection compared with WLC alone. Current data support an additional role in the reduction of recurrence of NMIBC. Since the approval of HAL by the FDA in 2010, experience of HAL–BLC in the USA continues to expand. To define areas of need and to identify the benefits of HAL–BLC in clinical practice, a focus group of expert urologists specializing in the management of patients with bladder cancer convened to review the clinical evidence, share their experiences and reach a consensus regarding the optimal use of HAL–BLC in the USA. The focus group concluded that HAL–BLC should be considered for initial assessment of NMIBC, surveillance for recurrent tumours, diagnosis in patients with positive urine cytology but negative WLC findings, and for tumour staging.

Daneshmand, S. *et al. Nat. Rev. Urol.* **11**, 589–596 (2014); published online 23 September 2014; doi:10.1038/nrurol.2014.245

Introduction

Bladder cancer is one of the most frequently diagnosed tumours worldwide: an estimated 74,690 new diagnoses were expected to be made and 15,580 deaths were estimated in the USA in 2014.[1] Although most patients are diagnosed at a relatively early stage, with non-muscle-invasive bladder cancer (NMIBC), the risk of dying from high-grade NMIBC remains substantial. Disease prognosis is affected in part by the high risk of tumour recurrence: depending on the grade at initial diagnosis, up to 61% of patients with NMIBC will experience recurrence within the first year after initial resection, and up to 78% will experience recurrence within 5 years.[2] Moreover, patients with NMIBC are also at risk of progression to muscle-invasive bladder cancer (MIBC), with approximately 17% risk at 1 year and 45% risk at 5 years.[2] Owing to the high risk of both recurrence and progression, patients require regular follow-up monitoring with cystoscopy after transurethral resection of the bladder tumour (TURBT).[3,4] Both the high prevalence of disease and the need for intensive endoscopic surveillance make bladder cancer one of the most costly cancers to treat.[5]

Optimal management of bladder cancer begins with urine cytology and thorough cystoscopic assessment of the bladder. The current standard of care is white-light cystoscopy (WLC), which enables the urologist to map and resect all visible lesions. Tissue specimens are then sent for pathological review to confirm the diagnosis and define the pathological stage. Bladder tumours can display numerous gross morphological features, ranging from erythematous mucosa to papillary tumours or solid masses.[6] However, not all cancerous areas are readily visible using WLC. The current general recommendation, according to the guidelines of urological associations, is to biopsy any area of the urothelium with an abnormal appearance, or if patients have positive urine cytology but no evidence of bladder cancer on WLC, to take random biopsies from normal-looking mucosa.[3]

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Competing interests
S.D. declares that he has been a meeting participant and lecturer for Cubist and Endo. H.B.G. declares that he has served as a consultant for Telormedix and as a scientific advisor for Abbott Molecular and Heat Biologics. A.M.K. declares that he has received grant or research support from Abbott, FKD and Cubist and has served on membership, advisory committee or review panels for Sanofi, Photocure, and Taris. B.R.K. declares that he has served as a consultant for Dendreon, GTx and Photocure, is a stockholder of Axogen and has worked on a clinical trial for Dendreon. M.J.R. declares that he has served as a consultant advisor for Dendreon and has been involved in a clinical trial for Genomic Health. J.A.W. declares that he is an advisor for Photocure and Ipsen. G.D.S. declares that he has served as a consultant, scientific advisor and speaker for Photocure and KARL STORZ. The authors were reimbursed by Photocure and KARL STORZ Endoscopy-America for their attendance at the consensus meeting. The other authors declare no competing interests.

Table 1 | European expert recommendations and consensus opinion on HAL–BLC

Setting	Recommendation		Consensus			Rationale
	EAU[3]	ICUD–EAU[18]	Europe[36]	UK[35]	Nordic[38]	
To guide initial transurethral resection of the bladder and biopsy	✓	NR	✓	✓	✓	To improve detection and complete resection of tumours and to enable accurate disease staging
In patients with positive urine cytology but negative WLC	NR	✓	✓	✓	✓	To confirm the diagnosis by detecting hard-to-visualize tumours, such as CIS
To aid diagnosis of CIS	✓	✓	✓	✓	NR	To improve detection of CIS lesions, which might be missed on WLC
To assess suspected recurrence	NR	NR	✓	✓	✓	To confirm or correct errors in staging and identify any additional or residual tumours
During follow-up assessment of patients with high risk of recurrence (high-grade T1, CIS or multifocal lesions)	NR	NR	✓	(✓)	✓	To maximize the chances of early detection of recurrent or residual disease
In patients with repeat resection within 6 weeks after TURBT	NR	NR	✓	NR	NR	To ensure additional lesions have not been missed, particularly CIS
In patients who have received intravesical therapy (BCG)	NR	NR	✓	NR	NR	To monitor treatment response and identify persistent lesions that can lead to change in patient management
At first follow-up cystoscopy	NR	NR	NR	(✓)	NR	To assess response to therapy (needs to be balanced against increased risk of false positives)
During office-based examinations with flexible cystoscopy	–	–	(✓)	–	–	To guide biopsies
As a training tool	–	–	✓	–	✓	To improve the quality of resection

✓: recommended by the panel. (✓): panel believes there might be a role, but further research is required. Abbreviations: BLC, blue-light cystoscopy; CIS, carcinoma *in situ*; EAU, European Association of Urology; HAL, hexaminolevulinate; ICUD, International Consultation on Urological Diseases; NMIBC, non-muscle-invasive bladder cancer; NR, not reported; TURBT, transurethral resection of the bladder tumour; WLC, white-light cystoscopy.

Despite best efforts, the full extent of an individual patient's tumour burden can be difficult to confirm on WLC alone, as small 'satellite' tumours or areas of carcinoma *in situ* (CIS) might be missed.[7–15]

The presence of persistent tumour after initial TURBT has been suggested to contribute to the high tumour recurrence rates in patients with NMIBC. In a retrospective analysis of >1,000 patients, Sfakianos *et al.*[7] found that 44.3% of patients who did not have a repeat TURBT had evidence of tumour recurrence at 3 months, compared with only 9.6% of those who underwent repeat resection. The benefit of early repeat TURBT is likely to be multifactorial, owing to complete resection, more accurate tumour staging (resulting in more appropriate initial management) and improved response to intravesical therapy, compared with single TURBT.[14,16,17] The International Consultation on Urological Diseases (ICUD), the European Association of Urology (EAU) and the American Urological Association (AUA) recommend repeat TURBT after 2–6 weeks in specific situations.[3,4,18] For example, the EAU recommends repeat resection after incomplete initial TURBT, if no muscle is present in the specimen after initial resection (with the exception of low-grade Ta tumours and primary CIS), in all T1 tumours and in all high-grade tumours except primary CIS.[3] Despite evidence demonstrating benefit, repeat resection is performed in the extreme minority of patients. Analysis of Medicare data for approximately 62,000 patients who underwent TURBT indicated that <5% of patients underwent a repeat procedure as recommended.[16] These data suggest that the quality of initial cystoscopic evaluation and resection needs to be improved, to permit more accurate pathological assessment and, ultimately, more appropriate treatment planning. Improving the initial management of patients with NMIBC will hopefully translate into improvements in disease control and survival.

Blue-light cystoscopy (BLC), also known as fluorescence cystoscopy or photodynamic diagnosis, is an adjunct to WLC that provides clearer imaging of bladder cancer. The procedure involves instillation of a photosensitizer into the bladder before the cystoscopy. Following instillation, the photosensitizer induces the preferential accumulation of protoporphyrins in rapidly proliferating cells, such as those in malignant bladder tumours, where protoporphyrins are converted to photoactive porphyrins, which fluoresce red when illuminated with blue light with a wavelength of 360–450 nm.[19] Hexaminolevulinate (HAL; marketed as Hexvix/Cysview by Photocure, Norway) is the only agent that has been approved in the USA and Europe for BLC photosensitization. Although 5-aminolevulinic acid (5-ALA) has been used in some clinical studies, it has not been approved by any health authorities, so we have focused on discussion of BLC using HAL (HAL–BLC).

To share experiences of using this technology, and to provide advice for other urologists considering adopting HAL–BLC in their routine management of patients with NMIBC, an expert focus group meeting was held in San Diego, USA, on 3 May 2013. The meeting involved 17 board-certified urologists with expertise in the management of patients with bladder cancer and varying levels of familiarity with HAL—ranging from those

Box 1 | US consensus recommendations and rationale on the use of HAL–BLC

At initial TURBT on suspicion of NMIBC

- Clinical trial evidence shows that HAL–BLC increases detection of bladder tumours compared with standard WLC: in a meta-analysis of nine trials involving a total of 2,212 patients, 20.7% of patients with primary cancer had at least one Ta or T1 tumour detected by BLC that was not detected by WLC (P<0.001)

In patients with positive urine cytology but negative WLC findings

- Positive cytology is probably a result of CIS, and HAL has been shown to detect more CIS than WLC does: in 527 confirmed cases of CIS, HAL identified 215 that were not seen on WLC[30]

In patients with intermediate-risk NMIBC

- Patients with multiple low-grade tumours, who have an intermediate risk of recurrence, present a management challenge because it can be difficult to identify and remove all lesions
- HAL–BLC increases detection of multiple tumours in individual patients and decreases the rate of recurrence[22]

For assessment of disease recurrence

- The meta-analysis of HAL–BLC trials indicated a significant benefit in detecting recurrent tumours compared with WLC alone:[30] 27.7% of patients with recurrent tumours had at least one Ta or T1 tumour detected by BLC that was not detected by WLC (P<0.001)

Following BCG instillation

- In the US licence, false-positive fluorescence with HAL–BLC is stated as a limitation with patients who have received BCG within the previous 90 days: evidence shows, however, that even within 60 days of BCG administration, BLC can detect lesions not seen on WLC, while the false-positive rate is no worse with BLC than with WLC[46]
- The risk of false positives seems to decrease over time, with increasing experience using HAL–BLC
- As the benefit from diagnosing clinically significant disease could outweigh the risk from unnecessary biopsy of false-positive fluorescence, the decision to use HAL–BLC should be made on a patient-by-patient basis

Abbreviations: BLC, blue-light cystoscopy; CIS, carcinoma *in situ*; HAL, hexaminolevulinate; NMIBC, non-muscle-invasive bladder cancer; TURBT, transurethral resection of the bladder tumour; WLC, white-light cystoscopy

Box 2 | HAL–BLC aids diagnosis when urine cytology is positive, WLC negative

A 67-year-old man with a history of low-grade NMIBC was referred for assessment. Despite positive urine cytology, extensive evaluation revealed no abnormalities on WLC including random bladder biopsies. Surveillance cystoscopy at 3 months was also unremarkable. However, urine cytology was positive at 3 months. Subsequent evaluation with HAL–BLC was performed, identifying a focal area of fluorescence on the posterior wall, where no abnormality was visible on WLC. The lesion was resected and sent for pathological analysis, which revealed the presence of CIS. The patient received induction and maintenance BCG therapy, resulting in no further evidence of disease, and negative cytology.

Abbreviations: BLC, blue-light cystoscopy; CIS, carcinoma *in situ*; HAL, hexaminolevulinate; NMIBC, non-muscle-invasive bladder cancer; WLC, white-light cystoscopy.

involved in the clinical trials (with >10 years experience) to those who had no practical experience with the agent. By including this range of experts, the focus group was able to consider the feasibility of the proposed uses for HAL–BLC in patients with NMIBC in the USA.

In this Expert Consensus Document, we review the existing evidence supporting the use of HAL–BLC and summarize the European recommendations for the use of this technology in patients with NMIBC (Table 1), before providing our expert opinion on the role and utilization of HAL–BLC in the management of bladder cancer in the USA (Box 1).

Hexaminolevulinate blue-light cystoscopy

Clinical trials and meta-analyses

The use of HAL–BLC during bladder tumour resection has been shown to translate into clinical benefit in five prospective international clinical studies involving nearly 1,800 patients.[20–25] In these studies, the use of HAL–BLC alongside WLC consistently increased detection rates of NMIBC lesions (especially CIS) compared with WLC alone, and accumulating evidence indicates that improved detection translates into reduced and delayed disease recurrence.[20–26] In the largest international, randomized controlled trial of HAL–BLC yet performed in patients with NMIBC, Stenzl *et al.*[24] reported a statistically significant reduction in recurrence rates at 9 months (47% for patients who received HAL–BLC and WLC compared with 56% for those who underwent WLC alone; P = 0.026), and a reduction in the rate of recurrent 'worrisome' tumours (defined as CIS, recurrent T1 or muscle-invasive disease; 16% versus 24%; P = 0.17). Most of the patients in this trial (93% of the WLC group and 94% of the HAL–BLC group)[24] were monitored for an extended period after completion of the primary analysis. Further analysis—after a median follow-up duration of 53 months for patients who underwent WLC alone and 55 months for those who received HAL–BLC in addition to WLC—revealed that the HAL–BLC group experienced a significant delay in median time to recurrence (16.4 months) compared with the WLC group (9.4 months; P = 0.04).[26] The proportion of patients in whom disease progressed to MIBC, and the cystectomy rate, were numerically lower in the HAL–BLC group (3.1% of patients developed T2–T4 disease, 4.8% had cystectomy) compared with the WLC group (6.1% and 7.9%, respectively), but these differences did not achieve statistical significance. This study was not, however, powered to detect differences in the risk of muscle invasion and cystectomy.[26]

In 2012, Shen *et al.*[27] reported a meta-analysis of 14 studies (12 of which were randomized controlled trials [RCTs]) involving a total of 4,078 patients with suspected or proven NMIBC. Although this analysis demonstrated lower residual tumour rates after BLC than WLC, detection was not better (relative risk [RR] 0.82; P = 0.07), and short-term recurrence-free survival and progression-free survival showed no significant difference between imaging modalities. The major limitation of this analysis was that 10 of the 14 studies included patients who received BLC with another photosensitizer, 5-ALA, which has not been approved by any health authority and which is known to be inferior to HAL for the detection of bladder cancer.

Another meta-analysis of 12 RCTs[28] revealed a lower recurrence rate for BLC (HAL–BLC or 5-ALA–BLC) than for WLC (odds ratio [OR] 0.5; P <0.00001), and improved recurrence-free survival for BLC at 1 year (hazard ratio [HR] 0.69; P <0.00001) and 2 years (HR 0.65; P = 0.0004). The rate of progression to MIBC was not reduced (OR 0.85, P = 0.39). Again, this meta-analysis included five studies that used 5-ALA.[28]

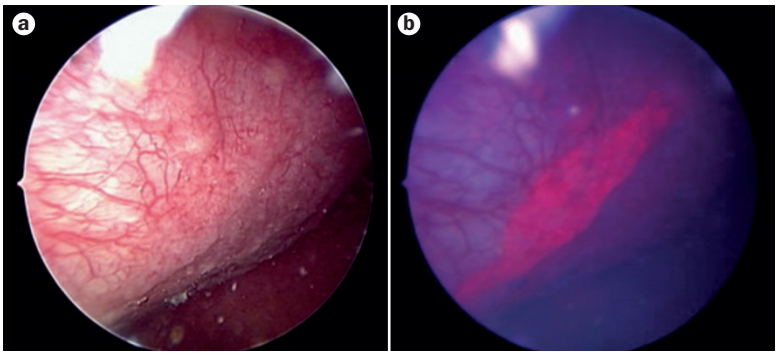

Figure 1 | HAL–BLC can detect recurrent NMIBC. A 77-year-old woman with a longstanding history of NMIBC—she had undergone office fulguration of 10 tumours over 5 years, all of which were pathologically confirmed as low-grade Ta lesions—was referred to our institution. She received five instillations of BCG and was unable to complete the sixth instillation because of severe irritative lower urinary tract symptoms. After 6 months she received three instillations of half-strength BCG. 3 months later, she again experienced recurrence, and sought a second opinion. She had HAL–BLC, and TURBT under anaesthesia in the operating room. **a** | A small area of potential tumour was identified on WLC. **b** | HAL–BLC revealed extensive (red) fluorescence corresponding to a large lesion. On pathological analysis, the lesion was found be CIS, which might have been in existence for some time. Abbreviations: BLC, blue-light cystoscopy; CIS, carcinoma *in situ*; HAL, hexaminolevulinate; NMIBC, non-muscle-invasive bladder cancer; TURBT, transurethral resection of the bladder tumour; WLC, white-light cystoscopy.

An RCT of patients who were all supposed to receive a single instillation of mitomycin C after TURBT demonstrated no statistically significant difference in 12-month recurrence rates between HAL–BLC and WLC (16% versus 22%, $P = 0.4$).[29] This lack of benefit with HAL–BLC is thought to be due to the fact that not all patients were treated according to the protocol, as more patients in the WLC arm received adjuvant mitomycin C than in the HAL–BLC group (77% versus 63%, $P = 0.04$). Also, in the HAL–BLC arm, more patients had high-risk NMIBC: 37% of patients assigned to receive HAL–BLC had stage pT1, G3 disease, compared with 25% of patients who received WLC. HAL–BLC was effective at detecting 'occult' CIS, with secondary CIS lesions identified in 26% of patients in the HAL–BLC group compared with 14% of patients in the WLC group.[29] Several independent groups have reported their own experiences of HAL–BLC (see Supplementary File online for references). Although many of these studies were small, single-institution or retrospective analyses, the results are consistent with the apparent superiority of HAL–BLC over WLC for the detection of bladder cancer.

A meta-analysis was conducted to pool the data on BLC from nine prospective trials that included only HAL and not 5-ALA.[30] In addition, this meta-analysis used raw data from the respective clinical trials and not just the published data, which makes it especially accurate and clinically relevant. All of these trials included patients with known or suspected NMIBC (Ta, T1 or CIS), who underwent HAL–BLC. Within-patient comparison was performed for tumour detection and between-patient comparison was performed to identify differences in the risk of tumour recurrence. HAL–BLC was associated with lower recurrence rates at 12 months compared with WLC (35% versus 45%; RR 0.761; $P = 0.006$). The benefits were independent of the baseline risk of recurrence and were demonstrated in patients with primary or recurrent Ta, T1 or CIS lesions.[30]

As a result of the positive outcomes of the clinical trials that demonstrated the efficacy and safety of HAL–BLC,[21–24] HAL was licensed by the European Medicines Agency (EMA) in Europe in 2005, and is indicated for use "as an adjunct to standard white light cystoscopy to contribute to the diagnosis and management of bladder cancer, in patients with known or high suspicion of bladder cancer."[31] The agent was licensed by the FDA for use in the USA in 2010 on the basis of the international phase III trial by Stenzl *et al.*,[24] and is indicated "for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy."[32] HAL–BLC is not approved as a replacement for random biopsies or other procedures used for the diagnosis of NMIBC.

False-positive rates

Some researchers have reported false-positive results for HAL–BLC, particularly in patients who have undergone recent TURBT, who have concurrent UTI or inflammation, or who have recently received intravesical BCG or chemotherapy. However, the most recently completed international phase III study by Stenzl *et al.*,[24] in which cystoscopy was performed ≥3 months after intravesical therapy, demonstrated similar false-positive rates for HAL–BLC (12%) and WLC (11%). In an earlier meta-analysis of BLC studies (not all of which used HAL as the photosensitizer), Kausch *et al.*[33] found that the difference in false-positive rates between BLC and WLC was generally small, ranging from 2% to 11%. Furthermore, the reported false-positive rates of BLC seem to be decreasing over time as experience with the technology increases.[34–36]

Safety of HAL–BLC

Most adverse events reported in the pivotal trial by Stenzl *et al.*[24] were mild or moderate in intensity, related to the procedure rather than to HAL itself, and were similar in the two treatment arms. The most common serious adverse events in both groups were haematuria (2.6% for HAL–BLC and 16.8% for WLC) and urinary retention (1% for HAL–BLC and 3.7% for WLC).

To date, the postmarketing surveillance safety data from the marketing authorization holders (Photocure and Ipsen, France) of >200,000 procedures (including some cases of multiple uses within the same patient) show adverse drug reactions in 28 cases.[37] Adverse events that were not considered to be related to HAL–BLC, but that could be caused by underlying disease or procedural complications, were reported in 41–58% of patients. No additional toxicity or anaphylactic reactions have been reported for repeated use of HAL in the same patient.[37]

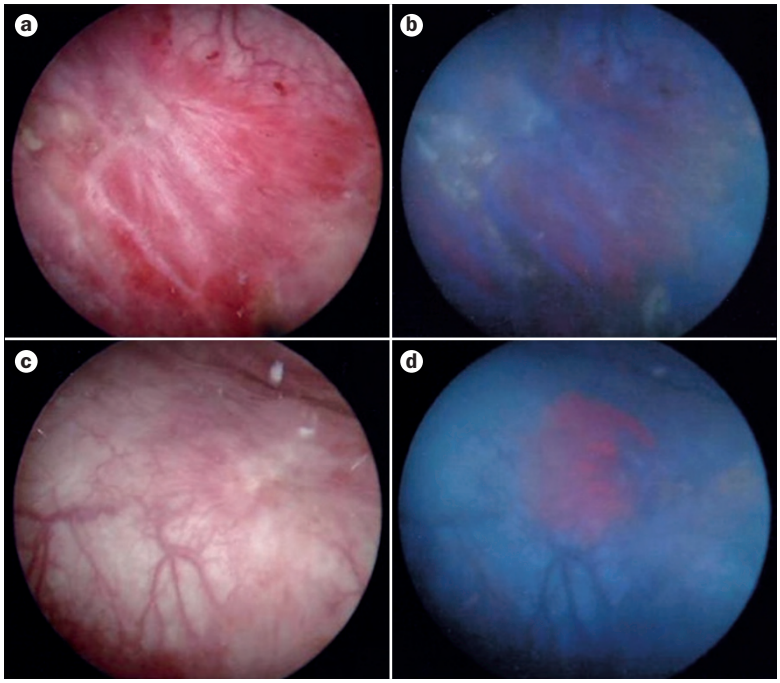

Figure 2 | HAL–BLC can help to confirm the diagnosis of high-grade tumours. A 65-year-old woman presented with gross haematuria. She had undergone cystoscopy at another hospital, where she had been diagnosed with high-grade papillary urothelial carcinoma. She was observed without intravesical therapy, and underwent follow-up WLC at 3 months, which showed suspicious lesions. The pathology from the biopsy reported "High-grade dysplasia and marked atypia worrisome for early TCC in patient with history of TCC." She sought a second opinion, and a decision on whether to undergo intravesical BCG or further surveillance. She was taken into the operating room for cystoscopy under white and blue light. Under WLC, the site of earlier biopsy was highly erythematous, which could have been caused by inflammation or scarring from previous biopsies. **a** | High-grade papillary urothelial carcinoma lesions were difficult to distinguish on WLC. **b** | HAL–BLC enabled diagnosis of high-grade papillary urothelial carcinoma lesions. **c** | CIS with pagetoid spread was indistinguishable on WLC. **d** | HAL–BLC enabled diagnosis of CIS with pagetoid spread. Note that the presence of residual urine can make for a poorer image quality. The patient is now receiving BCG therapy. Abbreviations: BLC, blue-light cystoscopy; CIS, carcinoma *in situ*; HAL, hexaminolevulinate; TCC, transitional cell carcinoma; WLC, white-light cystoscopy.

European experience and recommendations

Existing evidence has provided a basis for recommendations on the use of HAL–BLC by several expert groups in Europe (Table 1). These recommendations provide specific details and guidance for urologists, to complement the EMA-licensed indication for HAL. For example, the EAU bladder cancer guidelines recommend HAL–BLC for use "in patients who are suspected of harbouring a high-grade tumour, for example, for biopsy guidance in patients with positive cytology or with a history of high-grade tumour."[3] In addition, both the EAU and the second ICUD–EAU international consultation on bladder cancer conclude that HAL–BLC should be used to aid in the detection of CIS, including in patients with positive urine cytology but normal WLC (Table 1).[3,18]

Several European expert panels of urologists with experience using HAL–BLC have published consensus statements on settings in which this technology should be considered (Table 1).[35,36,38] These groups agree that HAL–BLC should be used in the initial assessment of suspected NMIBC, because increasing tumour detection can improve resection, reduce the risk of recurrence and delay the time to recurrence, thereby improving outcomes compared with WLC alone. Furthermore, in patients with positive urine cytology but negative WLC, HAL–BLC might identify hard-to-visualize lesions, such as CIS, and improve the yield of endoscopic evaluation.[35,36,38]

HAL–BLC should be used for all patients previously diagnosed with NMIBC who are under evaluation for suspected recurrence, but especially patients who initially had high-grade, multiple tumours, or with a suspicion of CIS.[36] HAL–BLC is recommended 6 weeks after completion of BCG induction therapy, to identify persistent lesions and to assess response to treatment and ensure accurate staging, to guide ongoing management decisions.[3,36] In patients who undergo repeat resection within 6 weeks of initial TURBT, HAL–BLC is recommended, to find additional tumours, especially CIS. Finally, Witjes *et al.*[36] propose that HAL–BLC has value as a teaching tool, helping to improve the quality of TURBT among urology trainees.

Use of HAL–BLC in the USA: expert consensus

Familiarity with HAL–BLC in the USA has been increasing since HAL was licensed by the FDA in 2010, and the prior European experience and recommendations have provided a valuable foundation on which to build US clinical practice. The San Diego expert focus group meeting of 3 May 2013 was convened to share experience with this technology and to generate transferable advice for those considering the use of HAL–BLC. The focus group considered various clinical scenarios and indications for the use of HAL–BLC in the USA, based on published data, the US licensed indication and the European expert recommendations and consensus opinions (Table 1). Case studies were presented to illustrate clinical scenarios for which the addition of HAL–BLC changed the management of the patient.

Q *What is the role of HAL–BLC in patients with positive urine cytology, but negative WLC findings?*

Patients with positive urine cytology, but negative WLC findings, present a clinical dilemma for urologists (Box 2). Previously, one had to perform additional procedures, such as bilateral ureteroscopy, prostate biopsies and random bladder biopsies to look for the source of the positive cytology. With HAL–BLC the source can be easily identified.

As recommended in the EAU and ICUD guidelines,[3,18] HAL–BLC is likely to be beneficial in patients with positive urine cytology but negative WLC findings, by increasing detection of hard-to-visualize lesions, such as CIS. The consensus panel believes that experience of HAL–BLC in US clinical practice has confirmed that the technology has value in such patients, by verifying the diagnosis and enabling the patient to receive optimal

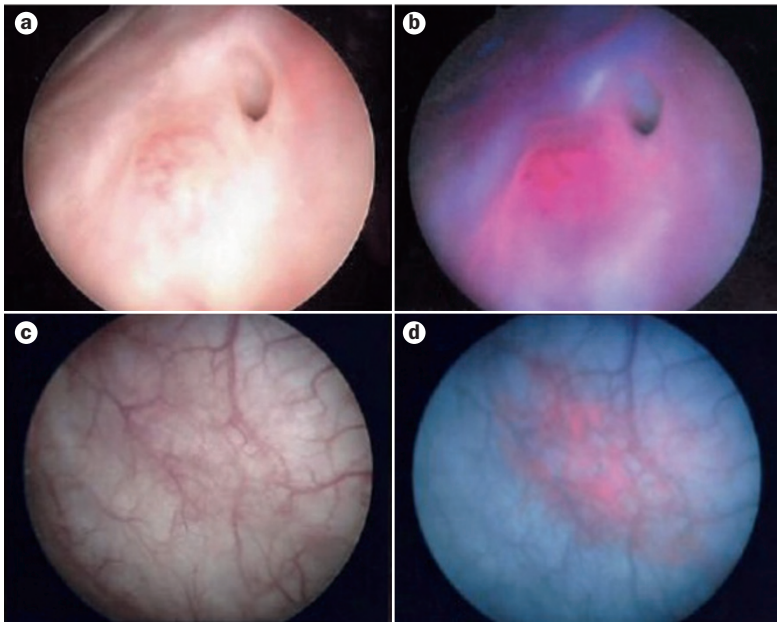

Figure 3 | HAL–BLC can help to diagnose tumour recurrence after intravesical therapy. A 63-year-old woman presented with gross haematuria and underwent HAL–BLC and TURBT. She was confirmed to have high-grade T1 urothelial carcinoma. Repeat TURBT after 6 weeks, using WLC only, was negative and she underwent a 6-week course of induction therapy with BCG. 8 weeks after completion of BCG therapy, the patient underwent repeat TURBT with HAL–BLC, which revealed fluorescence at the site of initial resection, as well as a secondary lesion not seen on WLC. The patient was diagnosed with high-grade T1 and CIS, and was recommended to undergo radical cystectomy owing to the significant risk of disease progression to muscle invasion and metastasis. **a** | WLC at the time of third resection did not detect a high-grade T1 lesion. **b** | The lesion was revealed by HAL–BLC. **c** | WLC did not detect CIS at the time of third resection. **d** | HAL–BLC detected a CIS lesion. Abbreviations: BLC, blue-light cystoscopy; CIS, carcinoma *in situ*; HAL, hexaminolevulinate; TURBT, transurethral resection of the bladder tumour; WLC, white-light cystoscopy.

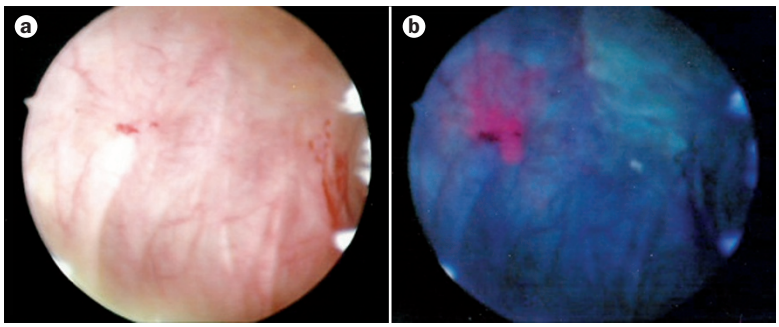

Figure 4 | HAL–BLC can assist restaging following intravesical therapy. A 68-year-old man diagnosed with high-grade Ta urothelial carcinoma was treated with a 6-week course of induction BCG. 8 weeks after completion of BCG therapy, the patient underwent repeat evaluation with HAL–BLC. **a** | Biopsy under WLC might have missed the extent of this tumour. **b** | HAL–BLC revealed progression of the tumour, with fluorescence at the site of initial resection, and a more extensive lesion that was not seen on WLC. The patient was diagnosed with high-grade T1 carcinoma and was advised to undergo radical cystectomy. Abbreviations: BLC, blue-light cystoscopy; HAL, hexaminolevulinate; WLC, white-light cystoscopy.

treatment (Box 1). The panel concluded that positive cytology is often caused by CIS, and that HAL–BLC has demonstrated a superior ability to detect CIS compared with WLC.

Q *What is the role of HAL–BLC in identifying recurrence in patients with CIS?*

Patients who present with recurrence but no evidence of CIS on WLC are often difficult to manage. HAL–BLC can detect CIS at recurrence when it is not anticipated (Figure 1). HAL–BLC has been shown to increase detection of both low-grade and high-grade tumours.[22] In patients with low-grade tumours, the likelihood of recurrence might be increased if multiple tumours or areas of concomitant CIS are present and unidentified. In these patients, the ability of HAL–BLC to identify additional lesions is of particular value, enabling complete TURBT, more accurate disease staging (if CIS is determined to be present) and improved management. The panel concluded that HAL–BLC has proved beneficial in detecting recurrent tumours, compared with WLC alone.

Q *What is the role of HAL–BLC in confirming the diagnosis of high-grade tumours?*

HAL–BLC can confirm the diagnosis of high-grade tumours, resulting in more appropriate management decisions. For example, in patients who have recently undergone TURBT, re-evaluation often reveals various stages of healing and inflammation. HAL–BLC can aid in targeting suspicious areas for biopsy, for better diagnosis and staging. High-grade lesions that are difficult to distinguish on WLC can be identified on BLC (Figure 2).

Q *What is the role of HAL–BLC after intravesical therapy?*

The diagnosis of disease recurrence after BCG therapy is critical in directing optimal management. Despite initial concerns that recent resection or intravesical therapy might increase the false-positive rate, data now show that ≥3 months after intravesical therapy, false-positive rates are similar for WLC and HAL–BLC.[24] In the clinical scenario discussed at the meeting, HAL–BLC after BCG therapy not only revealed fluorescence at the site of initial resection, but also secondary lesions (Figure 3). The patient was diagnosed with high-grade T1 lesion and CIS and was recommended to undergo a cystectomy given the high risk of progression. Similarly, HAL–BLC can be used to accurately stage bladder cancer after BCG therapy (Figure 4). In this case, the patient was treated with a 6-week course of BCG for high-grade Ta disease. 8 weeks after completion of BCG therapy, the patient underwent endoscopic evaluation, which revealed more extensive lesions than seen on WLC. Resection of the area revealed high-grade T1 carcinoma and the patient was advised to undergo cystectomy.

Consensus summary

The consensus opinion of the US expert group is in line with the opinions of European colleagues, namely that HAL–BLC has a role in the initial diagnosis of patients suspected to have NMIBC, as well as for recurrent bladder cancer (Box 1).[3,35,36,38] This opinion is based

Box 3 | Factors to consider when incorporating HAL–BLC into routine practice

Economic considerations

Improved detection and reduced risk of recurrence is associated with lower overall costs compared with WLC

Availability of HAL–BLC might lead to an increase in the number of patients seeking referral to the hospital

Stakeholder identification and communication

A multidisciplinary team approach involving pharmacy, nursing and operating room staff is required along with early engagement of the patient to achieve the efficient usage of HAL–BLC

Agreement on the use of HAL–BLC

HAL–BLC should be used in all appropriate patient types within the institution

Abbreviations: BLC, blue-light cystoscopy; HAL, hexaminolevulinate; NMIBC, non-muscle-invasive bladder cancer.

on the extensive evidence that HAL–BLC is associated with significantly increased detection rates for both primary and recurrent NMIBC lesions, compared with WLC alone.[30]

Q *How should HAL–BLC be incorporated into routine clinical practice?*

The consensus panel discussed the key factors that must be addressed when considering adoption of HAL–BLC (Box 3). As HAL–BLC requires initial investment in equipment, purchasing decision-makers will need to understand the business case for adoption of this technology, based on cost-effectiveness as well as clinical evidence. Training is required in order to perform HAL–BLC, and although the technique can be learnt with as few as five cases,[24] estimates of the learning curve suggest that 20 cases are required to achieve good interobserver agreement with an experienced operator, with 30 cases required to achieve proficiency.[34]

Pharmacoeconomic analyses from Europe and the USA indicate that the use of HAL–BLC leads to overall cost savings, because patients are likely to have longer recurrence-free intervals and, therefore, require fewer or less frequent TURBT than patients who receive WLC only.[39–44] In a probabilistic decision-tree model, Garfield *et al.*[39] concluded that use of HAL–BLC for the diagnosis of NMIBC could reduce the cost of care over 5 years compared with WLC (total cost US$25,921 versus US$30,581, respectively, excluding the cost of equipment acquisition). Estimates of the lifetime cost to treat bladder cancer range from US$96,000 to US$187,000 (at 2001 values) per patient in the USA.[44] In a study by Malmström and colleagues,[40] it was concluded that a potential saving of SEK1,321,716 (approximately US$190,000 at 2014 values) could be achieved in the Swedish health service if HAL–BLC was used in conjunction with WLC for all TURBTs in the first year after diagnosis of bladder cancer. Similarly, cost benefits of HAL–BLC in the German health service have been calculated as €168 per patient per year,[43] or, overall, €1,405, €2,245 and €1,738 per patient for patients in low-risk, intermediate-risk and high-risk groups, respectively.[41]

Practical advice on the use of HAL–BLC in US clinical practice has been published by Mark *et al.*[19] The technique requires cystoscopic equipment capable of emitting both white and blue light at the required wavelengths (with a range of 360–450 nm). Currently, only the D-Light C Photodynamic Diagnostic system (KARL STORZ Endoscopy-America, USA) has been approved for use with HAL in the USA. HAL is provided in a kit as 100 mg of powder that is reconstituted with 50 ml diluent before instillation. Once the solution is prepared, it must be used within 2 h. The timing of HAL preparation should be discussed with the pharmacy to ensure that processes are in place to permit timely instillation, which is particularly important for cystoscopies performed early in the morning. For instillation, the bladder is emptied via a catheter and the HAL solution is instilled into the bladder. Following instillation, HAL induces the preferential accumulation of protoporphyrins in rapidly proliferating cells, such as malignant bladder tumour cells, where protoporphyrins are converted to photoactive porphyrins, which fluoresce red when illuminated with blue light.[45] The patient must retain the solution in the bladder for 1–3 h to ensure optimum fluorescence. Thus, patients must be told to arrive early to allow time for instillation and retention of HAL. The nursing team requires training and information to ensure that they understand the instillation requirements for HAL and that they can advise patients on expectations. After HAL has been retained for ≥1 h, the patient is taken to the operating room and prepared for rigid cystoscopy under general or spinal anaesthesia. The bladder is initially inspected and mapped under white light and then reviewed under blue light using 30° and/or 70° ureteroscopes. As tangential viewing can result in fluorescence artefacts, the scope should be kept perpendicular to the bladder wall. Resection and biopsy should be performed under white light, because blue light can affect depth perception, but a final check of the completeness of the resection should be performed under blue light.[19]

Conclusions

Extensive evidence and clinical experience show that HAL–BLC can improve the detection of NMIBC beyond that achieved with WLC, which is the current standard of care. As a result, patients can benefit from a more complete TURBT and more accurate staging, resulting in more appropriate management decisions, with reduced risk of recurrence and prolonged time to recurrence. On the basis of data from clinical trials, European recommendations, and our own experience using HAL–BLC, the consensus of the US expert panel is that this technology is likely to be of benefit in a number of settings. Use of HAL–BLC should be considered both in the initial assessment of suspected NMIBC and in surveillance for recurrent tumours. In particular, HAL–BLC can be used to confirm the diagnosis of patients with positive urine cytology but negative WLC findings. In patients with low-grade disease, HAL–BLC can be used to detect multifocal lesions, reducing the risk of recurrence, and in patients with high-grade disease, improved detection using HAL–BLC can ensure that patients receive appropriate ongoing treatment and follow-up monitoring.

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Acknowledgements

This article is based on the Consensus Conference on Blue Light Cystoscopy with Cysview, which was sponsored by Photocure and KARL STORZ Endoscopy-America. Throughout the process, the authors retained full editorial control of the content and the decision to publish the article in *Nature Reviews Urology*.

Author contributions

All authors contributed to researching the data for the article, discussing content, writing the article and reviewing/editing the manuscript before submission.

Supplementary information is linked to the online version of the paper at www.nature.com/nrurol.