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ARTICLE

The diagnostic challenge of suspicious or positive malignant urine cytology findings when cystoscopy findings are normal: an outpatient blue-light flexible cystoscopy may solve the problem

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ABSTRACT

Purpose: To investigate whether outpatient blue-light flexible cystoscopy could solve the diagnostic challenge of positive or suspicious urine cytology findings despite normal white-light flexible cystoscopy results and normal findings on computerized tomography urography, in patients investigated for urothelial cancer.

Material and methods: In a multicentre study, a total of 70 examinations were performed with the use of blue-light flexible cystoscopy (photodynamic diagnosis) after intravesical instillation of the fluorescence agent hexaminolevulinate. The examination started with a conventional white-light flexible cystoscopy and then the settings were switched to use blue light. Suspicious lesions were biopsied. Afterwards, the patients were interviewed regarding their experience of the examinations.

Results: Bladder cancer was diagnosed in 29 out of 70 (41%) cases, among them 14/29 (48%) had malignant lesions seen only in blue light. The majority had carcinoma *in situ* (21/29). Normal findings were seen in 41 cases that underwent BLFC. During the further course, malignancy of the bladder was detected in six cases (9%) and malignancy of the upper urinary tract was detected in one case (1%). The majority of patients (93%) preferred the blue-light flexible cystoscopy performed at the outpatient clinic instead of the transurethral resection under general anaesthesia.

Conclusion: Blue-light flexible cystoscopy at the outpatient clinic may be a useful tool to solve unclear cases of a malignant or suspicious urinary cytology suggestive of bladder cancer. The procedure was well tolerated by the patients.

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Introduction

Bladder cancer is among the most common cancers worldwide [1]. About 70% of these tumours are non-muscle-invasive bladder cancer at the time of diagnosis. These tumours have a high tendency to recur (50%) and may progress to muscle-invasive or metastatic disease (9%) within 5 years of diagnosis [2]. The relative risk of progression increases with higher tumour stage and grade groups. When malignancy of the bladder is suspected, the majority of tumours are detected with conventional white-light flexible cystoscopy (WLFC) and computerized tomography (CT) urography [3]. Urine cytology is used as an adjunct to cystoscopy and CT urography. The sensitivity of cytology varies with tumour grade; being high for high-grade lesions (about 90%), but low in low-grade lesions. The specificity of urine cytology is high (about 90%) [4].

A few patients present with the diagnostic challenge of normal WLFC findings, a normal CT urography and positive urine cytology findings. In accordance with international guidelines [5], the next step would be a further investigation with transurethral resection of the bladder (TURB) with resection biopsies from suspicious, but also from normal-looking mucosa, and in males the prostatic urethra. However, the reliability of detection of carcinoma *in situ* (CIS) by 'blind mapping', that is, systematic random biopsies of normal-looking mucosa is limited [6–8]. If no tumour is detected in the bladder or urethra, positive or suspicious cytology findings are suggestive of upper tract urothelial carcinoma (UTUC), and the next step is selective sampling for cytology and retrograde ureteropyelography or -scopy. These procedures are associated with the risk of side-effects and are expensive as they are performed in the operating theatre under general anaesthesia [9–12].

The use of photodynamic diagnosis (PDD) in conjunction with TURB is now widespread. Flat lesions, that is, CIS and small papillary lesions may be difficult to detect with WLFC. Instead of 'blind mapping' the biopsies can be taken under the guidance of PDD after a porphyrin-derived photosensitizer, hexaminolevulinate (HAL), is instilled into the bladder. HAL accumulates in highly proliferating tumour cells and emits red light upon blue light excitation [13]. Studies have shown that TURB with PDD is more sensitive than conventional TURB for the detection of malignant tumours of the bladder, especially CIS [14,15]. The use of PDD may also

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Table 1. Demographics and characteristics of enrolled patients.

Demographics and characteristics	*n*
Study	Multicenter prospective observational study
Source population	Adults in Sweden and Denmark
Study period	January 2016 to December 2020
Median age, range (years)	74, 58–90
Male	52
Female	14
Tumour stage at original diagnosis	
Ta Low grade	7[a]
Ta High grade	19[b]
T1	14[c]
T2	1
CIS	14[a,b,c]
No previous bladder cancer	16
Previous intravesical treatment	
BCG	25
Mitomycin C	7

[a]Includes one patients with concomitant TaLG and CIS; [b]includes four patients with concomitant TaHG and CIS; [c]includes three patients with concomitant T1 and CIS.

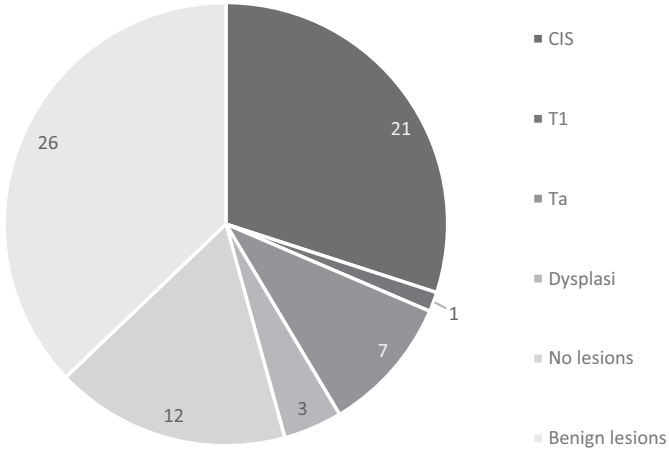

Figure 1. The total tumour detection rate with BLFC presented as tumour stage in 70 cases.

reduce residual tumour rates and increase recurrence-free survival [16,17]. According to previous studies, blue-light flexible cystoscopy (BLFC) in the outpatient setting with on-site biopsy and fulguration appears to be feasible, and allows early detection of recurrent lesions [18–21].

In this multicentre study, we investigated whether BLFC, applying a combination of white light and fluorescence with HAL, could increase the detection of bladder cancer already at the outpatient clinic by studying a group of patients with positive or suspicious urine cytology findings of unknown origin.

Methods

Patients

In 66 patients with urine cytology findings suggestive of malignancy, normal CT urography and normal WLFC, examinations with BLFC were offered at the outpatient clinic. The procedures were performed at four Swedish hospitals: Uppsala University Hospital, Helsingborg Hospital, Ljungby Hospital and Varberg Hospital, and one Danish Hospital; Lillebelt Hospital, during the period 2016–2020. To date, more than 500 BLFC procedures have been registered from the five clinics. We use BLFC for several indications, and cytology suggestive of malignancy and normal WLFC is one of them. Indications for urine cytology and cystoscopy were follow-up for bladder cancer, suspicion of primary cancer due to haematuria or irritative lower urinary tract symptoms. The patient characteristics are given in Table 1. Four patients underwent BLFC twice, due to the recurrence of abnormal cytology findings more than a year after the initial examination.

The urinary cytology was examined by the local pathologist and regarded as positive when the cells were assessed as malignant. The cytology was regarded as suspicious when cellular atypia with characteristic features suspicious for malignancy or if malignancy could not be excluded.

Cystoscopy

Fifty millilitres of HAL was instilled in the urinary bladder 1 hour before cystoscopy. At two of the centres, 10 ml 2% lidocaine (w/v) was included in the instillation as an anaesthetic. At one centre, a local anaesthetic was injected submucosally in the case of fulguration. Otherwise, only gel-anaesthesia including lidocaine was instilled into the urethra. Cystoscopy was performed by a urologist specialising in bladder cancer and with long experience of PDD. Flexible high-definition videoscopes were used with a blue and white light source from Richard Wolf or Karl Storz, Germany. The urethra and the bladder were first examined in white light, and tumours and any suspicious areas were recorded. The examination was then carried out in blue light, and fluorescing lesions were documented. Biopsies were obtained through the flexible cystoscope with oval cup biopsy forceps (EndoJaw, Olympus) with a working diameter of 1.9 mm. The biopsies were histologically examined by the local pathologist. Small tumours or localised CIS were fulgurated by electrocautery or diode laser in the same session. In the case of negative BLFC, it was possible to obtain selective cytology from the upper urinary tract using ureteral catheters 5 Charrier, length 100 cm (Boston Scientific). Any adverse events were recorded. After cystoscopy, the patients were asked to describe their individual experience as either 'Painful' or 'Not painful'. They were also asked whether they would have preferred to do the BLFC procedure at the outpatient clinic or the TURB procedure in the operating theatre under general anaesthesia.

Data collection

Data were collected prospectively in an online multicentre register. The patients signed an informed consent form allowing their data. The Nordic Blue Light Flexible Cystoscopy registry is an ongoing observational prospective study including patients undergoing BLFC with HAL in the outpatient clinic for suspicion of, or in routine follow-up for non-muscle-invasive bladder cancer. Data recorded are patient demographics, bladder cancer history, findings under BLFC, treatment performed and patient preference. In addition to data from the registry, electronic medical records and pathology reports were reviewed and additional details from further procedures were recorded. After treatment for bladder cancer, patients were scheduled for follow-up with cystoscopy, according to international guidelines.

Table 2. Findings at 70 blue light flexible cystoscopy procedures.

	Cytology		
	Malignant cells	Suspicious cells	Total
Histology			
Malignant (total)	10	19	29
Detected in blue light only	4	10	14
CIS	9	12	21
Detected in blue light only	4	7	11
Ta/T1	1	7	8
Detected in blue light only	0	3	3
Dysplasia	1	2	3
Detected in blue light only	0	1	1
Benign (total)	6	20	26
Detected in blue light only	3	8	11
None (no biopsy)	4	8	12
Total	21	49	70

Table 3. Results of 96 blue-light flexible cystoscopy guided biopsies.

Cytology	Malignant cells	Suspicious cells	Total
Biopsy result			
CIS	13	12	25
Detected in blue light only	6	8	14
Ta/T1	2	8	10
Detected in blue light only	1	3	4
Dysplasia	1	7	8
Detected in blue light only	1	4	5
Normal	7	29	36
Detected in blue light only	4	11	15
Inflammation	5	8	13
Detected in blue light only	1	5	6
Hyperplasia	0	4	4
Detected in blue light only	0	0	0

Results

Tumour detection

Bladder cancer was diagnosed in the outpatient setting using BLFC in 29 out of 70 cases (41%) and the majority (21/29) had CIS. In 14/29 (48%) cases, the malignant lesion(s) was seen only in blue light. The total tumour detection rate with BLFC and tumour stage are presented in Figure 1 and Table 2. Small Ta tumours were fulgurated on-site in five cases. All cases of CIS were later treated with BCG. Three cases of exophytic tumour were referred for TURB due to high-grade histology. A total of 96 lesions were biopsied, 60 lesions were non-malignant: normal or inflammation in 47, hyperplasia in five and dysplasia in eight. For details see Table 3.

Urothelial malignancy in patients with normal WLFC and BLFC findings

No suspicious lesions were found in 12 cases. Biopsies of suspicious lesions revealed benign histology in a further 26 cases, in total 41/70 cases with negative BLFC. Subsequently, the following diagnostic procedures were performed: Six patients underwent mapping biopsies in general anaesthesia including the prostatic urethra, revealing bladder cancer in four cases. Nine patients underwent selective urine cytology sampling, either in conjunction with BLFC (6 cases), or in the operating theatre (3 cases). Abnormal findings at selective urine cytology were further investigated with ureteropyeloscopy in three cases, and one case was diagnosed with UTUC. Three patients were treated with BCG solely based on cytology findings and a history of CIS in the bladder. During the following 12 months, a further two cases of urothelial malignancy were detected. In 31 cases (44%), no urothelial tumour was diagnosed during regular follow-up every 3–4 months with cystoscopy and urine-cytology the following year. A summary of the findings is given in Table 4. The decision to investigate further was based on cytology (malignant vs suspicious), individual patient factors (age, symptoms, comorbidity, smoking history) and the history of urothelial cancer.

Patient experience

Six patients complained of discomfort due to bladder distension, and in one of these cases cystoscopy could not be completed. Four patients experienced the pain associated with the biopsy and fulguration. One patient remained at the hospital for observation for a few hours due to haematuria following biopsy. All but one patient were discharged shortly after the examination. No allergic reactions or serious adverse events were noted. When interviewed, 51/55 (93%) of the patients stated that they preferred the BLFC procedure performed at the outpatient clinic, over TURB. Eleven patients could not take a stand on this issue.

Discussion

In this multicentre study, the use of BLFC resolved 41% of problematic cases suggestive of bladder cancer. In particular, a high rate of CIS was found, in agreement with previous studies. The BLFC outpatient procedure described here was simple and fast and was preferred by the majority of the patients. The conventional investigational path when positive or suspicious urine cytology of unknown origin includes TURB and investigation of upper urinary tracts. These are invasive procedures performed under general anaesthesia, being both time-consuming and demanding for the patient and associated with greater risk of complications and mortality and higher costs [9–11,21]. Here we investigate a new, minimally-invasive method that is with minimal risk and discomfort for the patients and yields valuable results in the form of early diagnosis of bladder cancer and recurrence.

Concerning earlier studies of TURB with blue light (PDD), Schmidbauer et al. [15] evaluated 211 patients, 83 having CIS, of whom 18 (22%) were detected only in blue light. Stenzl et al. [17] studied the detection of Ta or T1 tumor at TURB in blue light and found a relative reduction in the recurrence rate of 16%, during the 9-months follow-up. Hermann et al. [18] studied BLFC at the outpatient clinic and found in 20/73 (27%) patients additional tumour lesions that were not identified in white light (five CIS, 15 Ta). Zare et al. [19] identified 14 patients as having histologically confirmed tumour using BLFC. Three patients had tumours identified in blue light only (two with Ta, and one with CIS), 11 could be managed on-site with fulguration, whereas three were referred to the operating room. Daneshmand et al. [20] studied BLFC for surveillance of 103 patients. In 13 of the 63 patients (20.6%), recurrence was seen only in blue light. Five of these cases are confirmed as CIS. Drejer et al. [21] studied 699 patients in a randomized routine surveillance trial with

Table 4. Follow-up of patients with negative blue light flexible cystoscopy (normal or benign histology).

Diagnostic procedure	Total	Positive	Findings
Mapping biopsies (general anaesthesia)	6	4	CIS in two patients, TaG1 in one patient, TaG3 of the prostatic urethra in 1 patient.
Selective cytology	9	4	Positive in two patients, suspicious in two patients.
Ureteroscopy	3	1	In one patient an UTUC was found in the renal pelvis.
Follow-up cystoscopy only	19	2	Two patients developed bladder cancer stage T1 and CIS within 12 months.
None	7		Dismissed or no follow-up.

The table shows further investigation or follow-up of cases not diagnosed with bladder malignancy at BLFC. All cases that underwent ureteroscopy had performed selective cytology sampling.

BLFC vs WLFC after TURB for NMIBC. They concluded that the use of BLFC at the first follow-up after TURB reduced the risk of a later tumour recurrence. These previous studies are all in accordance with our results.

When cytology indicates malignancy, urologists may tend to take biopsies more liberally, which may explain the high number of benign lesions biopsied. Inflammatory lesions have an increased uptake of HAL, which may be mistaken for malignant lesions [22]. Dysplastic lesions were regarded as benign. In fact, dysplasia has architectural features resembling those of malignant cells and is believed to be precancerous in 15–19% of lesions [23] Adenocarcinoma originating from the prostate may be misdiagnosed as urothelial neoplasm in cytology. Although prostate cancer is rarely detected by urine cytology, it may present with abnormal cytological findings, normal BLFC findings and a diagnosis of advanced prostate cancer [24].

Various imaging modalities can be used to facilitate the visualisation of bladder cancer, for example, Olympus Narrow-Band Imagining [25], the Storz Professional Image Enhancement System, and autofluorescence. A real-time multispectral imaging method combining different techniques has also recently been reported [26]. Each method has advantages and limitations. PDD has been in use the longest and is the best validated of all the methods. The urologists participating in this study were very experienced with PDD during both TURB and BLFC, which is why this technique was used in this study.

If our method with BLFC did not reveal any malignancy, the patients were further investigated according to guidelines. Thus, no patients were put at hazard for not being properly investigated. Patients with multifocal CIS or CIS near the bladder neck as well as high-grade tumors underwent a further TURB including biopsies of the prostatic urethra. In case of no malignancy at the BLFC, a normal finding from the selective urine cytology sample taken during the BLFC-procedure could limit further examinations of the upper urinary tract. A few cases of 'false negative' results were found with BLFC, demonstrating that the sensitivity of BLFC is not 100%. They were detected with 'blind mapping'. These patients were highly selected with a history of high-grade bladder tumour and positive cytology findings.

A potential shortcoming of the method proposed here lies in the examination of the urethra, as tangential blue light can make normal mucosa appear fluorescent. Nevertheless, we found two lesions with BLFC in the prostatic urethra that were not detected with WLFC alone. The capability to retroflect with BLFC is excellent for the evaluation of the bladder neck and trigone.

Cytology is used as an adjunct in the diagnosis and follow-up of urothelial malignancy. The interpretation is user-dependent. The cellular yield and preservation of cells may play a role, too. Bladder wash cytology is typically considered to be more sensitive than cytology of voided urine. However, for practical purposes, the voided specimen continues to be of value, first because it is non-invasive and easy to obtain and, second because it may detect upper tract or urethral tumours [27]. The specificity has not been altered significantly by different sampling techniques. Positive cytological findings have high specificity for high-grade tumours, while suspicious cytological findings are less specific. A large proportion of negative BLFC findings in this study were preceded by suspicious cytological findings, which could be due to reactive atypia. Others may be explained by precancerous lesions, and therefore careful follow-up is required. Follow-up of patients with cellular atypia depends on risk factors for urothelial malignancy. How to handle patients with suspicious cytology but negative cystoscopy? Patients with repeat suspicious cytology or symptoms have a significantly higher risk of urinary malignancy than those with normal urine cytology carried out 6–8 weeks later. Patients with persistent suspicious cytology may need further evaluation and follow-up. Asymptomatic patients with negative repeat cytology may not require further evaluation [28].

The patients' subjective ratings provided a measure of how they perceived the examinations. Discomfort due to distension of the bladder can be reduced by the suction device of the cystoscope. The instillation of local anaesthetics probably has no effect on discomfort due to distension, but it may relieve pain associated with biopsy and fulguration. Local submucosal injection of anaesthetic would probably alleviate the pain of fulguration, and may also alleviate an *en bloc* laser resection of a bladder tumour. The level of pain was low throughout the study, in agreement with recently published findings [20,29]. These are registry data, not individual interviews, so more research is necessary to clarify this issue. A forehand selection was made because patients not willing to perform the BLFC in local anaesthesia would not enter the registry. The majority of the patients still preferred the BLFC procedure over TURB.

Conclusions

BLFC at the outpatient clinic with local anaesthesia may solve many unclear cases of a malignant or suspicious urinary cytology in a simple and rapid way. The procedure is well tolerated and generally preferred by patients.

Ethical approval

The study was approved by the Ethics Committee in Uppsala, Sweden (Reg. No. 2016/036) and by the Danish Data Protection Agency (Reg. No. 16/5384). The study was performed in accordance with good clinical practice and the Declaration of Helsinki.

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Disclosure statement

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