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Concurrent bladder cancer in patients undergoing photodynamic diagnostic ureterorenoscopy: how many lesions do we miss under white light cystoscopy?

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Introduction There is an ongoing debate on panurothelial changes in the upper and lower urinary tract as multifocal presentation of urothelial cancer is well recognised. Concurrent bladder cancer impacts the outcome of the upper urinary tract urothelial cancer treatment, while its detection still relies on the white light cystoscopy.

Material and methods We retrospectively reviewed all patients who underwent photodynamic diagnostic ureterorenoscopy, choosing those who had synchronous bladder biopsies. Each patient received 20 mg/kg body weight of oral 5-Aminolevulinic acid around 3–4 hours before endoscopy. All procedures were performed by a single endourologist experienced in photodynamic diagnosis and flexible ureterorenoscopy.

Results Between July 2009 and June 2013, 69 patients underwent bladder biopsies at the time of photodynamic diagnostic endoscopic inspection of the upper urinary tract. In total, 43.5% (30/69) patients were found to have bladder lesions, of which 43.3% (13/30) were proven to be carcinoma in situ. White light inspection of the bladder missed bladder cancer in 16 (23.1%) patients, of which 12 were carcinoma in situ. There were 14 bladder cancer lesions missed under white light which were concomitant to the upper urinary tract urothelial cancer. Twelve (17.4%) patients developed minor complications relevant to the photosensitizer.

Conclusions The study raises a concern about missing small bladder cancer/carcinoma in situ lesions on the initial diagnosis or in surveillance of the upper urinary tract urothelial cancer. Higher than previously reported, the rate of concomitant bladder cancer may suggest utilisation of photodynamic diagnosis to ensure the cancer free status of the bladder, but this needs to be ratified in a multi-institutional randomised trial.

Key Words: 5-aminolevulinic acid ‹› photodynamic diagnosis ‹› cystoscopy ‹› ureterorenoscopy ‹› urothelial neoplasms ‹› ureteral neoplasms

INTRODUCTION

Upper urinary tract urothelial cancer (UUT UC) is a rare lesion accounting for approximately 10% of all renal and 5% of all urothelial tumours [1, 2, 3]. The natural history of UUT UC is not fully understood. There is ongoing debate whether multifocal presenation of urothelial cancer (UC) suggests panurothelial (wide spread) cancerous changes in the upper and lower urinary tract. Previous/synchronous bladder cancer appears to have a significant effect on the recurrence free rate and outcomes following the treatment of UUT UC [4, 5, 6]. There is an association of bladder cancer (BC) with ureteric and multifocal UUT UC. Liang suggested that previous or concomitant non-muscle invasive bladder cancer

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was a significant risk factor of high grade UUT UC confirmed in a nephroureterectomy specimen [7]. The presence of more advanced UUT UC has been reported if concomitant BC is confirmed. Synchronous BC does not influence cancer-specific survival following treatment of UUT UC. It does however increase the risk of intravesicle recurrences [8, 9]. Previous or concomitant BC is a significant predictor of recurrence [10]. It is therefore essential to perform a panurothelial endoscopy in patients under surveillance following treatment of UUT UC.

Although BC is one on the most important predictors of UUT UC treatment outcome, its detection relies on white light cystoscopy. To increase detection, the European Association of Urology (EAU) guidelines recommended PDD cystoscopy if CIS or high grade BC is suspected [11]. PDD increases detection, improves treatment and reduces the risk of recurrence of BC. Furthermore, PDD can identify CIS that may have been missed on white light [11]. The use of PDD cystoscopy is advised as part of the routine inpatient endoscopic surveillance to confirm the efficacy of treatment and to identify any previously missed or recurrent tumours [12].

The principle of PDD is the interaction between light and a fluorophore such as Protoporphyrin IX, which has high accumulation in tumour cells. The light is absorbed by the fluorophore and then re-emitted at a longer wave length which could then be easily detected [13, 14, 15]. Two photosensitizers have been used for the photodynamic diagnosis of bladder cancer: 5 Aminolevulinic Acid (5-ALA) and its ester, Hexyl Aminolevulinate (HAL). Both agents have been found to be similar in terms of sensitivity and specificity [13, 16].

When investigating possible bladder tumours the photosensitizer is usually instilled into the bladder directly, however, this can be time consuming. This method only allows the use of PDD in the bladder whereas the use of systemic (oral) photosensitizer is needed when investigating the upper tract. We have previously demonstrated our success in investigating UUT UC with 5-ALA given orally 3–4 h before the planned ureterorenoscopy [17, 18]. Therefore, we believe it is feasible to detect synchronous multifocal upper and lower urinary tract tumours using this method.

White light cystoscopy, a standard tool in the assessment of the bladder at the time of primary diagnosis of UUT UC, remains insufficient to depict all urothelial lesions within the bladder. Photodynamic diagnosis is acknowledged to achieve a better bladder mucosal visualisation and improves the detection of exophytic lesions by 20% and carcinoma in situ (CIS) by 39% [9]. The aim of the study is to assess the detection rate of concomitant BC during photodynamic diagnostic ureterorenoscopy. We investigated the diagnostic accuracy of detecting bladder tumours concurrently and / or incidentally found during diagnosis and surveillance of patients with suspected / proven UUT UC using oral 5-ALA.

MATERIAL AND METHODS

Retrospective review of all patients who underwent photodynamic diagnostic ureterorenoscopy (PDD-FURS) was carried out. Between July 2009 and June 2013, sixty nine patients underwent bladder biopsies at the time of PDD endoscopic inspection of UUT. Patients' demographics are demonstrated in Table 1. Of these patients, twenty five underwent initial diagnostic ureterorenoscopy and forty four had surveillance ureterorenoscopy for UUT UC. Cytological assessment of urine sampled from the bladder is of questionable value in the detection of UUT UC. Therefore, the test was not used routinely.

Caldicott approval was granted and the lead consultant (collecting data) was registered with the National Information Commissioner's Office.

Each patient received 20 mg/kg body weight of oral 5-ALA (Medac, Scion House, Stirling University Innovation Park, Stirling, UK) dissolved in 50 ml of water, 3–4 hours before surgery. For palatability, the mixture was further added to 100 ml of juice.

All procedures were performed by an endourologist experienced in photodynamic diagnosis and ureterorenoscopy. The patients served as their own controls. Local protocol was followed. Each procedure was

Table 1. *Patients' demographics*

Number of patients	69
Age median (range)	73 (50-85)
Sex	
Male	54
Female	15
Smoking status (had lesions):	
Ex-Smoker	20 (11)
Current Smoker	31 (13)
Non-Smoker	18 (6)
Previous UC (Cis):	
Lower urinary tract	10 (6)
Upper urinary tract	28 (0)
Lower and upper urinary tract	8 (5)
Pathological findings:	
Benign	22
Inflammation	17
Cis (concomitant to UC)	13 (1)
Dysplasia (concomitant to UC)	2 (2)
Cancer	18

UC – urothelial cancer; Cis – Carcinoma in situ

Table 2. *Findings on diagnostic (suspicion of upper urinary tract urothelial cancer) photodynamic diagnostic ureterorenoscopy*

Computed thomography urography findings	History of bladder cancer	Smoker	Presence of bladder cancer (pathology)		Presence of upper urinary tract cancer (pathology)	
			White light	Blue light	White light	Blue light
Filling defect – calyx	no	ex	no (benign)	no (benign)	no (benign)	no (benign)
Filling defect – pelvis	no	yes	no (Cis)	yes (Cis)	yes (pTaG2)	yes (pTaG2)
Normal	no	ex	no (benign)	no (benign)	no (benign)	no (benign)
Filling defect – pelvis/ureter	no	ex	no (benign)	no (benign)	yes (pT1G3)	yes (pT1G3)
Thickening – ureter	no	no	no (benign)	no (benign)	no (benign)	no (benign)
Filling defect – pelvis/calyx	yes pTaG3	ex	no (pTaG3)	yes (pTaG3)	yes (HG UC)	yes (HG UC)
Thickening – ureter	yes pT1G2	yes	yes (pTaG3)	yes (pTaG3)	no (benign)	no (benign)
Mass – ureter	no	yes	no (Cis)	yes (Cis)	yes (HG UC)	yes (HG UC)
Thickening – ureter	no	no	no (benign)	no (benign)	yes (benign)	no (benign)
Filling defect – calyx	no	no	no (benign)	no (benign)	no (benign)	no (benign)
Filling defect – ureter	no	yes	no (benign)	no (benign)	yes (pTaG2)	yes (pTaG2)
Normal	yes pTaG3	ex	no (Cis) Yes (pTaG2)	yes (pTaG2&Cis)	no (benign)	no (benign)
Mass – ureter	yes pTaG2	ex	no (benign)	yes (benign)	yes (pTaG2)	yes (pTaG2)
Filling defect –pelvis/calyx	no	yes	yes (benign)	yes (benign)	no (benign)	no (benign)
Normal	no	no	no (benign)	no (benign)	no (benign)	no (benign)
Filling defect – calyx	yes pTaG3/ Cis	no	no (benign)	yes (benign)	no (Cis)	yes (Cis)
Thickening – ureters bilaterally	no	no	no (benign)	no (benign)	no (benign)	no (benign)
Thickening – ureter	no	no	no (benign)	no (benign)	no (benign)	no (benign)
Normal	no	no	no (benign)	no (benign)	no (benign)	no (benign)
Stenosis – ureter	yes Cis	yes	no (dysplasia) yes (pTaG2)	yes (pTaG2& dysplasia)	no (LG UC)	yes (LG UC)
Filling defect – pelvis	no	no	no (benign)	yes (benign)	yes (HG UC G2)	yes (HG UC G2)
Mass – pelvicalyceal system	no	no	yes (pTaG2)	yes (pTaG2)	yes (pT1G3/Cis)	yes (pT1G3/Cis)
Filling defect – ureter	yes pTaG2	yes	yes (pTaG2)	yes (pTaG2)	yes (pTaG2)	yes (pTaG2)
Filling defect – ureter	no	ex	no (Cis)	yes (Cis)	yes (pT1G2)	yes (pT1G2)
Filling defect – pelvis/ureter Bladder mass	no	yes	yes (pTaG3)	yes (pTaG3)	no (benign)	no (benign)

started with rigid cystoscopy under standard white light followed by blue light endoscopy. After an assessment of the lower urinary tract, the flexible ureterorenoscopy (FURS) was performed with the similar pattern of white light and blue light inspection. All suspicious bladder lesions where biopsied and all tumours were treated regardless of the white or blue light use. Biopsies were taken from small lesions first to avoid being missed due to photobleaching effect. Random biopsies from the normal bladder walls were also taken. An experienced uro-pathologist reported the biopsy findings.

D-light system (Karl Storz, Tuttlingen, Germany) was used to detect fluorescence (Olympus PDD cystoscope with 30-degree telescope and Karl Storz PDD Flex-X^2 ureterorenoscope). Special fluorescence excitation light source (D-light-C, Karl Storz GmbH & Co. KG, Tuttlingen, Germany) was used with a protoporphyrin IX excitation filter permitting the blue-violet light (380–430 nm) and a fluid light cable (495 FS, Karl Storz GmbH & Co. KG, Tuttlingen, Germany) to ensure a much higher transmission, mainly in the blue spectral range in comparison to a standard glass fiber bundle. The fluid light cable also blocks the infrared light generated by the light source. An ocular of cystoscope / ureterorenoscope has a protoporphyrin IX cut-off filter (long pass filter) which blocks light below 450 nm in PDD-mode reducing almost the complete blue excitation light that is diffusely backscattered by the tissue. The capable fluorescence camera (Tricam II SL PDD pendulum camera head, Karl Storz GmbH & Co. KG, Tuttlingen, Germany) allows detection of the red fluorescence light with an increased sensitivity especially in the range between 600–700 nm. A control on the camera head for the cystoscope and ureterorenoscope allowed for switching between the white and blue lights with ease.

The diagnostic accuracy was calculated for white light (WL) and blue light (BL) cystoscopy by visualisation of the lesion and by correlation with the biopsy results to obtain True positive (TP), True negative (TN), False positive (FP), or False negative (FN) values. The sensitivity, specificity and accuracy for the correct detection of the lesion for each WL and BL were calculated. The resulting diagnostic accuracy figures where compared between the two groups (WL and BL cystoscopy). The analysis was done using the Meta-analysis of Diagnostic and Screening Tests 1.4 programme (Unidad de Bioestadistica Clinica, Hospital Ramon y Cajal, Madrid). P value <0.05 was considered statistically significant.

Table 3. *Diagnostic findings of photodynamic diagnosis (PDD) and white light cystoscopy*

White light cystoscopy	Positive (pathology) for tumor diagnosis	Negative (pathology) for tumor diagnosis
Abnormal	13	4
Normal	18	34
Blue light (PDD) cystoscopy		
Abnormal	29	16
Normal	1	23

RESULTS

In total, 43.5% (30/69) patients were found to have bladder lesions, of which 43.3% (13/30) were proven to be CIS. All the patients in this study were planned to have PDD ureterorenoscopy with only one bladder lesion detected on Computed Tomography Urography (CTU) prior to the procedure.

Twenty five patients underwent diagnostic PDD ureterorenoscopy (Table 2) for the abnormal findings on CTU (n = 21), persistent frank hematuria (n = 1), suspicion of distal ureteric cancer on TURBt (n = 1), abnormal cytology (n = 1) and for the assessment of contralateral UUT before nephroureterectomy (n = 1). Ten (40%) patients were diagnosed with BC, of which seven (70%) were concomitant to UUT-UC. Five (50%) of BCs were missed on white light cystoscopy of which four were concomitant to UUT. Four of undetectable lesions under white light was reported as CIS and one a solitary tiny high grade UC pTaG3. White light cystoscopy also missed a dysplasia (not classified as CIS) lesion concomitant to UC pTaG2. Two of bladder lesions missed by the white light were solitary (normal UUT). Seven patients had a past history of BC. Three of them were diagnosed with BC concomitant to UUT-UC and two had solitary UUT-UC on PDD ureterorenoscopy.

In the surveillance group (n = 44), twenty (45.4%) patients were diagnosed with BC, of which fourteen had a past history of BC. Ten (50%) BC lesions were concomitant to UUT-UC. White light missed eleven (55%) of all bladder cancers (9 of CIS and 2 small pTaG2 lesions) and one dysplasia lesion (not classified as CIS) concomitant to UC pTaG2. Seven of the missed lesions (63.6%) were concomitant to UUT UC. Blue light was statistically more sensitive in detecting bladder lesions, however, less specific (Tables 3, 4). Overall, cystoscopy during PDD ureterorenoscopy detected significantly more malignant lesions compared with the standard white light ureterorenoscopy (Table 4). In addition, blue light panurothelial endoscopy detected significantly more lesions, while white light missed all but one CIS bladder lesion

Table 4. *Comparison of white and blue light diagnostic accuracies*

	Sensitivity (95% CI)	Specificity (95% CI)	Total Detection rate % (N/TN)	CIS Detection rate % (N/TN)	UC Detection rate % (N/TN)
White light cystoscopy	41.9 (0.25-0.61)	89.5 (75.2-97.1)	43.3 (13/30)	7.6 (1/13)	67.7 (12/18)
Blue light cystoscopy	96.7 (82.8-99.9)	59 (42.1-74.4)	96.7 (29/30)	92.3 (12/13)	100 (18/18)
	P = 0.0001	P = 0.002	P = 0.0008	P = 0.001	P = 0.05

CI – confidence interval; N – number; TN – total number; CIS – carcinoma in situ; UC – urothelial cancer

(Table 4). There was no statistical difference between the two modalities regarding detection of urothelial cell cancer (Table 4). Diagnostic accuracy was 0.68 for white light and 0.75 for PDD cystoscopy, respectively (Table 3). Despite this, white light missed six of the eighteen lesions and blue light detected all of them (18/18).

DISCUSSION

There is an established link between BC and UUT UC. A study of patients who underwent radical nephroureterectomy between 1995 and 2010 revealed 9.4% incidence of concomitant and 12.5% of past history of bladder cancer. Of which, 31.4% of patients developed bladder cancer within 37.5 months after nephroureterectomy [8]. Furthermore, 28–29% of patients diagnosed with UUT UC have past history of bladder cancer [9, 16]. Another study reported that 80–90% of patients develop metachronous BC within 2 years from UUT UC diagnosis [19]. The high rate of intravesicle recurrences is either a consequence of missed bladder cancer on initial diagnosis or panurothelial manifestation of UC (panurothelial field defect). There is no evidence to support the higher risk of seeding into the bladder following diagnostic ureterorenoscopy. The reported bladder recurrence free survival for nephroureterectomy following diagnostic ureterorenoscopy was (60%) compared to (58.7%) in patients undergoing nephroureterectomy alone. Pre-nephroureterectomy ureterorenoscopy did not impact on cancer- free survival either [20]. Endoscopic ablation of the UUT UC also does not appear to increase the risk of seeding into the bladder [19].

It is well established that white light cystoscopy detects approximately 50% of CIS lesions only [21]. CIS is undersampled during routine treatment of BC and photodynamic diagnosis improves detection rate from 23–68% (white light alone) to 91–97% [22]. Missing CIS during cystoscopy may result in progression and higher risk of cancer specific death in up to 20–83% of patients [23]. In our report, twelve of the 13 CIS cases were found on PDD only. We confirm inability of standard white light cystoscopy during ureterorenoscopy to visualise CIS lesion, which is a high grade cancer with potential risk of progression and development of metastases. Precise detection of CIS during diagnostic or surveillance ureterorenoscopy will have a significant impact on the treatment and follow-up. PDD increased the detection rate of CIS in these patients, hence giving a higher accuracy for superficial cancer detection.

The use of PDD as a method for the detection of bladder cancer has been accepted by the EAU since 2006 [23]. Moreover, the use of photosensitizers during transurethral resection of bladder tumours allows for more complete resection and reduces the recurrence rate [25]. The photosensitizer, 5-Aminolevulinic Acid (5-ALA) can be administered as an intravesical installation or as an oral solution. Inoue et al. found that both routes were equally effective in detecting bladder lesions that were otherwise invisible when using the white light endoscopy [26]. Intravesical 5-ALA was installed for 1 to 3 hours while the oral solution is given to the patient 3 to 4 hours prior to the procedure [28]. In our cohort 5-ALA was only given orally as all of our patients were planned to undergo PDD visualisation of the UUT. It can be argued that oral administration of the photosensetizing agent would be preferable because this method does not require prior catheterisation of the patient. On the other hand, the solution needs to be given at an earlier stage before the procedure. Oral 5-ALA was used due to its proven effectiveness within the urothelium. The other photosensitizer, Hexaminolevulinate (HAL) is a hexyl-ester of 5-ALA with potential to produce at least twice the fluorescence of ALA in a lower concentration [24]. HAL, however, is a topical photosensitizer and cannot be used systemically and so therefore has a limited use for panurothelial endoscopy.

Our study has shown comparable results to PDD cystoscopy using intravesical installation [13]. The advantage of using oral 5-ALA is the ability to perform a simultaneous upper and lower urinary

tract PDD endoscopy in patients who have a high risk of multi-focal disease.

The false positive findings of PDD in the bladder is usually caused by different factors including hyperplasia, inflammation, previous intravesical treatment and inexperience in the use of PDD [27]. Patients who have had catheters or ureteric stents could develop areas of mucosal reaction which have a higher uptake of the photosensitising agent. These areas could appear suspicious on PDD and mask cancerous cells. None of our patients had urinary tract instrumentation or a ureteral stent for at least 4 weeks prior to the procedure and all procedures were carried out by a senior endourologist with experience in PDD.

A single dose intravesicle instillation of Mitomycin C following nephroureterectomy reduces the risk of bladder recurrences, with an absolute reduction in risk by 11% and the relative reduction by 40%. It is hypothesised that Mitomycin C prevents the implantation of the urothelial cancer cells exfoliated from the upper urinary tract [29]. Studies have suggested the ability of intravesicle chemotherapeutics to ablate solitary non-muscle invasive low grade bladder cancer [30]. Post nephroureterectomy instillation of Mitomycin C may be able to ablate small urothelial cancer lesions, which are not visualized on preoperative cystoscopy.

There are no studies investigating the incidence of bladder cancer concomitant to upper urinary tract urothelial cancer on enhanced visualization. Panurothelial PDD might influence the decision to give Mitomycin C post-operatively.

All together 43.5% of patients who underwent PDD ureterorenoscopy were found to have bladder lesions, of which 43.3% were proven to be CIS. We found that bladder inspection under blue light during PDD ureterorenoscopy with oral 5-ALA had higher sensitivity than white light cystoscopy (96.7%. 95% CI 82.8-99.9) but lower specificity (59%. 95% CI 42.1–74.4). Furthermore, though it did not reach statistical significance, PDD had a much higher detection rate, and so accuracy in the detection of CIS and dysplasia lesions which was clinically significant.

Specificity was low throughout the urinary tract. This is mainly due to high false positives which could be attributed to a number of factors, including the irritation from the catheter or stents, infections and inflammations, previous intravesical treatment or even inexperience in the use of PDD. This is not unexpected as cystoscopy was done in the naïve bladder in 33.3% cases (n = 23) only.

CONCLUSIONS

Our report is the first to present the results of blue light inspection of the bladder in a group of patients undergoing PDD ureterorenoscopy. Although the number of procedures is small, there is a raised concern about missing small bladder cancer/carcinoma in situ lesions on initial diagnosis or surveillance of UUT UC. Our data suggest the value of photodynamic diagnosis. Systemic administration of 5-Aminolevulinic Acid as a photosensitizer for PDD-FURS allows complete assessment of the upper and lower urinary tract urothelium (panurothelial endoscopy). The technique has a higher sensitivity and detection rate for cancerous lesions (especially for carcinoma in situ) of the lower, as well as, upper urinary tract compared with the white light alone. Higher than the previously reported rate of concomitant BC may suggest utilisation of PDD to ensure cancer free status of the bladder, but this needs to be ratified in a multi-institutional randomised trial.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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