

Oral 5-aminolevulinic acid in simultaneous photodynamic diagnosis of upper and lower urinary tract transitional cell carcinoma – a prospective audit

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Study Type – Therapy (case series)
Level of Evidence 4

OBJECTIVE

- To evaluate the diagnostic accuracy of photodynamic diagnostic ureterorenoscopy after oral administration of 5-aminolevulinic acid (5-ALA) for upper urinary tract urothelial cancers.

PATIENTS AND METHODS

- In this audit, twenty-six patients underwent thirty-nine procedures (cystoscopy/ureterorenoscopy) following oral administration of 5-ALA for photodynamic diagnosis (PDD).
- Twenty mg/kg body weight of 5-ALA was given orally 3–4 hours prior to the planned endoscopic visualisation.
- Following standard white light cystoscopy and ureterorenoscopy, photodynamic diagnostic endoscopy was performed using D-light system (Olympus PDD cystoscope and 7.5Fr KARL STORZ PDD Flex-X ureterorenoscope) to detect fluorescence.
- Biopsies were carried out from all suspicious areas, noting if lesions were detected under white or blue light or both.

RESULTS

- A total of sixty-two biopsies were performed for suspicious urothelial lesions

What's known on the subject? and What does the study add?

The idea of using photosensitizing agents to enhance visualization of cancer tissue dates back to 1900. 5-Aminolevulinic acid (5-ALA) was first suggested for photodynamic diagnosis (PDD) of transitional cell cancer (TCC) of the bladder in 1992. Since then, PDD with intravesical application of 5-ALA or its ester hexaminolevulinate (Hexvix) has proven to be superior over standard white-light cystoscopy in detection of carcinoma *in situ* and dysplasia as well as enhancing margins of TCC. PDD of upper urinary tract TCC is under-studied because of trouble with delivery of the photosensitizer. Fluorescence after oral 5-ALA was initially reported in 1956. Oral 5-ALA for photodynamic therapy was suggested for upper urinary tract TCC in 1998 and for refractory non-muscle invasive bladder cancer in 2001. A study in 2012 on oral and intravesical application of 5-ALA for bladder PDD showed no difference in diagnostic accuracy for each modality.

To our knowledge our series is the first report on use of oral 5-ALA for PDD in detection of upper urinary tract tumours. We published our initial results in 2010. We think that our recent audit is quite encouraging. PDD ureterorenoscopy resulted in detection of additional urothelial tumours that could have been missed by the conventional white-light endoscopy. We suggest that this technique should be used in large multicentre trials to replicate our results.

(35 bladder, 26 ureter/renal pelvis and 1 from prostatic urethra).

- Of the 35 bladder biopsies, 11 lesions were seen under both white and blue light and 91% of these were malignant.
- While 24 (68.5%) biopsies were taken from lesions seen only under blue light and 45.8% of these were malignant.
- Similarly, of the 26 ureteric/renal pelvicalyceal biopsies, 11 were concurrent in both white and blue light and 100% of these were malignant.
- While 10 (38.5%) lesions were seen only under blue light and 70% of these were malignant.

CONCLUSIONS

- Photodynamic diagnosis using oral 5-ALA is safe and feasible with additional advantages of detecting lesions not visualised with conventional white light endoscopy.
- This may translate into more complete treatment thereby decreasing subsequent recurrences and possibly progression of the upper urinary tract urothelial cancers.

KEYWORDS

photodynamic diagnosis, transitional cell carcinoma, ureterorenoscopy

INTRODUCTION

Transitional cell carcinoma (TCC) of the bladder is a common urological malignancy whereas upper urinary tract transitional cell carcinoma (UT-TCC) is infrequent, accounting for around 7% of urothelial tumours. Standard diagnostic modalities for these tumours are white-light endoscopy and radiological imaging. For UT-TCC, the role of pretreatment histological diagnosis is controversial. However, ureterorenoscopy with a brush or forceps biopsy is required in cases where the diagnosis is in doubt, or the management would be significantly altered by endoscopic findings [1].

White-light endoscopy can detect obvious and sizeable urothelial TCC whereas subtle mucosal lesions may be missed. Diagnosis of these occult lesions is important because these have important implications for disease progression and management decisions. Photodynamic diagnosis (PDD) is a step forward in enhancing diagnostic accuracy for urothelial TCC. Successful clinical application of the fluorescence has been reported in dermatology, brain, tracheobronchial tree and more recently in bladder tumours [2]. Kelly and Snell were the first to suggest that a haematoporphyrin-derivative could be used as an aid to the diagnosis and treatment of bladder cancers [3]. PDD uses fluorescence to localize these lesions by selective accumulation of protoporphyrin IX in the tumours. PDD cystoscopy has high sensitivity for detecting bladder tumours, in particular carcinoma *in situ* [4]. Both hexaminolevulinic acid and 5-aminolevulinic acid (5-ALA) induced PDD can enhance the diagnostic accuracy of cystoscopy for bladder carcinoma [5–10]. Additionally, PDD with these photosensitizers decreases the rate of recurrent non-muscle invasive bladder tumours by enhancing their initial diagnosis and treatment [8,11,12]. One-hour intravesical instillation of these agents is required 1 h before fluorescence cystoscopy, which is resource dependent and may not be available widely.

Diagnosis of UT-TCC is more challenging especially when radiological investigations are not conclusive. The use of blue-light-assisted ureterorenoscopy in UT-TCC is still in its early stages. We previously reported a short case series of oral administration of 5-ALA for PDD of UT-TCC [13]. Now we

TABLE 1 Indications for photodynamic diagnosis in study participants

Previous history of TCC		New patients (suspicious UT-TCC on CTU)	
Location of TCC	No. of patients	Location of TCC	No. of patients
Bladder TCC*	6	Renal pelvis	2
UT-TCC	4	Ureter	6
Both bladder and UT-TCC	8		

*TCC, transitional cell carcinoma; UT-TCC, upper tract transitional cell carcinoma; CTU, computed tomography urogram. *Patient with history of bladder tumours and a new suspicious UT-TCC on follow-up CTU.*

present a prospective audit of the results of a simple and practical technique of PDD for upper and lower urinary tract TCC using oral 5-ALA as photosensitizer. We aim to explore the role of 5-ALA in detecting abnormal tissues in the upper urinary tract.

PATIENTS AND METHODS

This prospective audit includes all patients who required upper urinary tract endoscopic assessment for diagnosis, treatment and follow-up for UT-TCC. The photodynamic diagnostic ureterorenoscopy was approved by the 'Improvement and Quality Committee' of our institute. All patients gave their consent before the procedures.

Each patient received 20 mg/kg bodyweight of 5-ALA (Medac, Stirling, UK) dissolved in 50 mL water, then mixed with 50–100 mL orange juice to flavour the drink. The mixture was given orally 3–4 h before the planned endoscopy [14]. After oral administration, patients were kept away from direct sunlight or strong room light for 24 h. This protocol was based on the Scottish Photodynamic Therapy Centre and the Scottish Adult Neurosurgical Network guidelines for the use of oral 5-ALA.

A single urologist performed all procedures. The technique of ureterorenoscopy and biopsy followed principles recommended by Tawfik *et al.* [15] and by Grasso *et al.* [16]. The bladder and upper urinary tract were mapped first under white light and then under blue light. Following standard white-light cystoscopy and ureterorenoscopy, PDD endoscopy was performed using a D-light system (Olympus PDD cystoscope with 12-degree and

70-degree telescopes and a 7.5 Fr KARL STORZ PDD Flex-X ureterorenoscopy) to detect fluorescence using a xenon arc lamp with a blue light with a 380–440 nm wavelength. Biopsies were carried out from all suspicious areas noting if lesions were detected by white or blue light, or both. Random biopsies from normal mucosa were taken from upper urinary tract only if reported as suspicious on CT urogram. Upper tract tumours suitable for endoscopic management (visible under white or blue light) were ablated with a holmium : YAG laser (with curative intent).

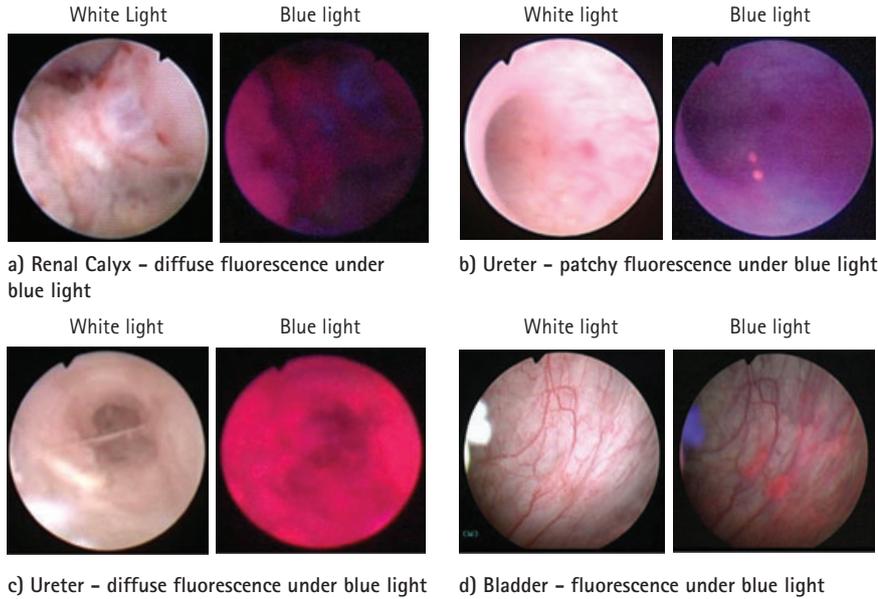
The biopsy specimens were fixed in formalin and processed as standard for haematoxylin & eosin staining. The WHO 1973 histological grading system and 2004 WHO consensus classifications are used in parallel in our institute.

Data were collected for all patients included in the study. The primary outcome variable of the statistical analysis was the difference in abnormal lesions seen under white and blue light endoscopically and pathological outcomes. MICROSOFT EXCEL 10.0 was used to manage and analyse the data.

RESULTS

Twenty-six patients were included in the audit with a mean (\pm SD) age of 70.3 years (\pm 11) and a male to female ratio of 22:4. The indications for PDD are summarized in Table 1. Thirty-nine procedures were performed using 5-ALA and 62 biopsies were taken, 35 from bladder, 26 from upper urinary tract, and one patient underwent diagnostic TURP for strong fluorescence from the prostatic urethra. During the study

FIG. 1. Comparisons of endoscopic visualization under white and blue light. (a) Renal calyx, diffuse fluorescence seen under blue light, biopsy confirmed pTaG2 transitional cell carcinoma. (b) Ureter – dot-like fluorescence, biopsy from these areas showed a carcinoma in situ. (c) Ureter – diffuse fluorescence under blue light, biopsy confirmed carcinoma in situ. (d) Bladder – biopsy from the fluorescence areas confirmed pTaG2 transitional cell carcinoma.



carcinoma *in situ*). Three biopsies (12.5%) showed dysplasia (Figs 1 and 2). Biopsy from prostatic urethra (diagnostic TURP) revealed pTaG3 TCC. Patients with negative biopsies were followed up with flexible cystoscopy, only if they had a history of bladder TCC.

Twenty-six biopsies were taken from renal pelvi-calyceal systems or ureters. Eleven of these biopsies were taken from lesions identified under both white and blue light and all of these were malignant. Five random biopsies were taken from mucosa with normal appearance in both white and blue light (reported as suspicious on CT urogram), all of which turned out to be benign. Ten biopsies (38.5%) were taken from the abnormal mucosal areas seen only in blue light (seven malignant pTaG2, two dysplasia and one benign) (Figs 1 and 2). The subsequent biopsy (after 3 months) in one ureteric dysplastic area was confirmed as pTaG2 tumour.

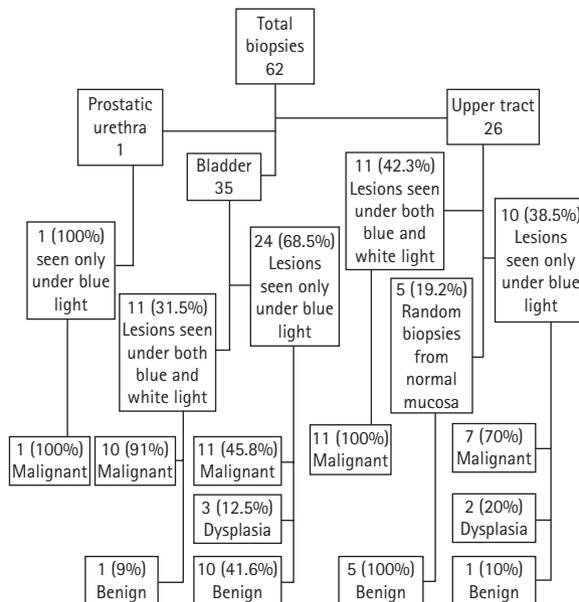
Biopsies from most (90%) of the fluorescent areas seen under blue light were abnormal (malignant or dysplasia). One patient with benign histology had a repeat CT urogram and urinary cytology at 6 months. Both investigations were normal.

Additionally, 10 upper urinary tract lesions were visible only under blue light. The corresponding CT urograms were reported as normal in half of these patients and urine cytology was suspicious (C4) in only one of these five patients. Hence, with standard white light ureterorenoscopy these tumours could have been missed.

The median operation time was 30 min (range 15–60 min). The variability of time was the result of the additional procedures required, i.e. cystoscopy +/- biopsy/resection of bladder tumour and ureterorenoscopy +/- biopsy/ tumour ablation +/- stent(s) insertion. The cost of 1 vial of 5-ALA (1.5 g) was £110. PDD cystoscopy was being used as a diagnostic tool in our institution before we implemented PDD ureterorenoscopy, so purchase of the 7.5 Fr KARL STORZ PDD Flex-X ureterorenoscope (approximately £12 000) was the only additional cost.

No major complications were seen in the audit cohort. Two patients developed transient asymptomatic hypotension before endoscopy and four patients developed a facial skin photosensitive reaction. The

FIG. 2. Algorithm of endoscopic findings and pathological results of bladder and upper tract biopsies.



period, 15 patients underwent PDD ureterorenoscopy once, nine patients had the procedure twice and two patients thrice.

Thirty-five biopsies were taken from suspicious bladder mucosal lesions and one from fluorescent prostatic urethra. Among the bladder biopsies, 11 (31.5%) were taken

from lesions seen with both white and blue light. Histological analysis showed that 10 (90.9%) of these biopsies were malignant. Twenty-four (68.5%) biopsies were taken from mucosal lesions seen under blue light only. Ten of these biopsies (41.6%) were benign while 11 biopsies (45.8%) were malignant (nine pTaG2, one pT1G3, one

patients were managed symptomatically and responded well without any long-term or serious outcomes.

DISCUSSION

We have shown that PDD ureterorenoscopy with oral 5-ALA is beneficial for the detection of malignant urothelial lesions that are not seen under standard white light. Appropriate management and prediction of prognosis of the urothelial TCC are dependent on careful endoscopic evaluation of the whole urinary tract. Concomitant urothelial tumours in the bladder and upper urinary tract, especially carcinoma *in situ*, are an important risk factor for tumour recurrence and progression [17–19].

In our audit, the oral 5-ALA-induced PDD ureterorenoscopy provided promising results in localization and detection of malignant urothelial lesions of the upper urinary tract as well as the bladder. Most of the blue-light-guided biopsies were malignant (70% upper urinary tract and 45.8% from the bladder). The higher percentage of positive biopsies from the upper urinary tract than from the bladder is possibly a result of the study population selected, which included patients with suspected UT-TCC or being followed up for UT-TCC. The aim of this audit was to investigate the role of oral 5-ALA PDD for UT-TCC diagnosis. However, additional bladder tumours were also depicted. This audit does not recommend systemic (oral) 5-ALA for PDD diagnosis of lower urinary tract lesions. Bladder TCC can be found using white-light cystoscopy in 8–13% at the time of diagnosis of UT-TCC and bladder recurrence rate varies between 17% and 47% after endoscopic treatment of UT-TCC [20]. We showed that the use of oral 5-ALA for PDD ureterorenoscopy allows simultaneous blue-light inspection of the bladder to diagnose small/occult concomitant bladder TCC.

In addition to the detection of overt malignant urothelial lesions, strong fluorescence was also observed in areas of urothelial dysplasia. The urothelial dysplasia is characterized by architectural distortion, variable degree of atypia and scanty mitotic activity in the basal and intermediate cell layers. Diagnosis of these dysplastic lesions is also clinically significant because there is

evidence that dysplasia shares some abnormalities with carcinoma *in situ* and has a high tendency to develop into cancer [21]. In this present audit, PDD ureterorenoscopy detected three dysplastic lesions in the bladder and two in the upper urinary tract, indicating that these precursor lesions can be identified during PDD ureterorenoscopy. These findings showed that simultaneous blue-light-assisted cystoscopy at the time of PDD ureterorenoscopy detects additional malignancies within the lower urinary tract that could be missed under white light. Hence the diagnostic credibility of PDD ureterorenoscopy was superior with oral 5-ALA use.

Localization and the reliability of the pathological specimens from upper urinary tract lesions remain the most important difficulties in UT-TCC ureteroscopic diagnosis. We have shown that the targeting of the upper urinary tract lesions was improved by PDD ureterorenoscopy. However, the biopsies were taken with standard ureteric biopsy forceps so no real improvement was observed in the quality of the specimens. In this audit, none of the specimens from the upper tract included muscular fibres, so pTa stage, or non-invasive papillary urothelial carcinomas, can be considered doubtful. Various authors considered that tumour grade could be just as predictive concerning disease evolution and prognosis of the patients [22]. Furthermore, it has been established that protoporphyrin IX concentration in the muscular layer of the bladder is minimal and PDD cannot be used as a staging tool [14].

Accurate and timely detection of the recurrent urothelial TCC is important to prevent tumour progression. Routine follow-up cystoscopy may not identify all recurrent bladder TCC [23]. In our audit, both new patients and those undergoing follow-up for UT-TCC were included. For both of these subgroups, detection of the abnormal mucosal lesions under blue light was superior to the standard white light endoscopy. However, its significance and its effect on management and long-term benefits for both new and follow-up patients need to be addressed in separate studies.

There are a few limitations to this paper that warrant mention. First, this is an

observational audit evaluating the concept that the oral 5-ALA-induced PDD ureterorenoscopy may improve detection of urothelial TCC. Although, the results are encouraging, randomized trials are required to establish the superiority of this newer technique over standard diagnostic modalities for UT-TCC. Second, this technique is operator dependent so estimation of the degree of fluorescence is questionable. A standard fluorescence grading system is required to overcome this issue. Furthermore, our data include both new ($n = 14$) and recurrent ($n = 12$) UT-TCC, and because of the small number of patients in these groups it is not possible to draw meaningful statistical differences in the role of PDD ureterorenoscopy for new and recurrent UT-TCC. Finally, because of the lack of long-term follow-up, correlation of this endoscopic diagnosis with more robust endpoints such as recurrence-free and overall survival could not be established.

In summary, PDD ureterorenoscopy seems to represent a valuable diagnostic technique for UT-TCC, showing considerable improvement of tumour visual accuracy as well as tumour detection rate. This may translate into more complete endoscopic treatment thereby decreasing subsequent recurrence and possibly progression. Further studies are needed to evaluate the role PDD in the diagnosis of the upper urinary tract lesions in addition to clarifying the impact of this technique on the recurrence rates and on tumour-free and overall survival.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: TCC, transitional cell carcinoma; UT, upper urinary tract; PDD, photodynamic diagnosis; 5-ALA, 5-aminolevulinic acid.