Arab Journal of Urology (2017) **15**, 100–109

Arab Journal of Urology
(Official Journal of the Arab Association of Urology)

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ONCOLOGY/RECONSTRUCTION
REVIEW

Photodynamic diagnosis in upper urinary tract urothelial carcinoma: A systematic review

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Received 31 October 2016, Received in revised form 8 December 2016, Accepted 23 January 2017
Available online 6 March 2017

KEYWORDS

Upper tract TCC;
Photodynamic diagnosis;
Blue light detection;
5-Aminolaevulinic;
Photodynamic ureteroscopy

ABBREVIATIONS

5ALA, 5-aminolevulinic acid;
CIS, carcinoma *in situ*;
CTU, CT urogram;
HAL, hexaminolaevulinate;
HNPCC, non-polyposis colorectal

Abstract ***Objective:*** To assess the diagnostic accuracy and safety of photodynamic diagnosis (PDD) in upper urinary tract urothelial carcinoma (UUTUC).

Materials and methods: A systematic literature search was conducted. Included studies were assessed for the risks of bias and quality using appropriate tools. Dedicated data extraction forms were used. Diagnostic accuracy in terms of sensitivity and specificity were quoted whenever provided by individual studies. A combined toxicity profile of 5-aminolevulinic acid (5ALA) was given after reviewing individual studies.

Results: In all, 17 studies were identified. After screening seven studies were included involving a total of 194 patients. None of the studies were randomised. All the available studies were of low-to-moderate quality. The largest available study, with 106 patients, reported a sensitivity of 95.8% and 53.5% for PDD and white-light (WL) ureterorenoscopy (URS) respectively, with a statistically significant difference. The specificity was 96.6% for PDD and 95.2% for WL-URS with no statistical significance. PDD showed better ability in detecting carcinoma *in situ* and dysplasia. One study compared PDD to computed tomography urogram (CTU) and found PDD to have better sensitivity and statistically significantly better specificity. 5ALA-associated toxicity was minor in nature and hypotension was the most common adverse event.

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Peer review under responsibility of Arab Association of Urology.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.aju.2017.01.003

carcinoma;
NBI, narrow-band imaging;
PDD, photodynamic diagnosis;
PPIX, protoporphyrin IX;
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses;
QUADAS, Quality Assessment of Diagnostic Accuracy Studies;
(UUT)UC, (upper urinary tract) urothelial carcinoma;
URS, ureterorenoscopy;
WL, white-light

Conclusion: PDD in UUTUC appears to be more accurate than WL-URS and CTU, with no significant toxicity. Larger scale randomised trials are needed.

Introduction

Upper urinary tract urothelial carcinoma (UUTUC) represents 5–10% of all UCs [1]. It tends to be twice as common in the renal pelvis and calyces as compared to ureteric in location. Despite different incidence rates, both UUTUC and bladder UC share the same risk factors, with concurrent upper and lower tract UC in 17% of cases [2]. The commonly shared avoidable risk factors include: tobacco consumption, industrial hazards related to certain carcinogens such as aromatic amines [3,4], as well as the use of the analgesic phenacetin, which was banned in 1970. There is some genetic predisposition to UUTUC. Hereditary UUTUC is associated with hereditary non-polyposis colorectal carcinoma (HNPCC). Screening for UUTUC is recommended in patients diagnosed with HNPCC before the age of 60 years and in cases that show familial aggregation [5–7]. Histologically, there are some variants of the UUTUC that are associated with less favourable prognosis and these include: micropapillary, plasmacytoid, small-cell carcinoma (neuroendocrine), and lymphoepithelial [8,9]. The most common presenting symptom of UUTUC is visible or invisible haematuria in up to 80% of cases [10]. Less commonly, flank pain and lumbar mass may be the presenting symptoms in 10–40% of cases [11]. Systemic symptoms such as weight loss, anorexia and cough are associated with metastatic disease. CT urogram (CTU) is the most accurate imaging method, with a sensitivity of (0.67–1.0) and specificity of (0.93–0.99) [12,13]. However, CTU is still regarded as suboptimal for flat lesions, e.g. carcinoma *in situ* (CIS) [14]. Similarly, urine cytology collected directly from the UUT is of some value in the diagnosis of UUTUC but with poor sensitivity for low-grade disease [15].

Diagnostic ureterorenoscopy (URS) can resolve uncertainties especially when combined with biopsy [16]. Recent advances in equipment technology has resulted in miniaturisation of ureteroscopes and the introduction of wide variety of flexible ureteroscopes with a large spectrum of capabilities in terms of deflection ability and better visibility [17].

The most recognised method for treating UUTUC is radical nephroureterectomy [18]. Nevertheless, ~40% of UUTUC are non-muscle invasive at presentation [19]. Therefore, nephron-sparing approaches in well-selected patients, with relatively early stages and less aggressive grades of malignancy, are justified [7]. Consequently, the impetus for improving the diagnostic tools to facilitate early detection has definitely risen.

One of these tools is the use of the photodynamic diagnosis (PDD). This is based on the visual aid provided by certain photosensitisers during UUT endoscopy. Photosensitisers are substances that make human tissue fluoresce to light at a specific wavelength. The commonly used photosensitisers in the diagnosis of UC are 5-aminolaevulinic acid (5ALA) and its hexyl ester, hexaminolaevulinate (HAL), both of which are porphyrin precursors. The process of conversion of porphyrin into heme is catalysed by the ferrochelatase enzyme. Malignant cells are deficient in ferrochelatase [20]. This leads to the accumulation of protoporphyrin IX (PPIX). When exposed to violet light of ~420 nm PPIX is seen as a red signal against a blue violet background making undetectable flat tumours and CIS visible.

The aim of the present review was to evaluate the effectiveness and safety of photodynamic substances in

the diagnosis of UUTUC. The review aimed to answer the following questions.

1. How effective is the use of photodynamic-assisted URS in the diagnosis of UUT TCC and CIS?
2. What is the extent of the toxicity associated with using photosensitisers?

Materials and methods

A comprehensive search was carried out using Medline, EMBASE, Google scholar and the CENTRAL trials registry of the Cochrane Collaboration using the following terms.

1. Photodynamic diagnosis AND upper urinary tract urothelial cancer.
2. 5-Aminolaevulinic acid AND the diagnosis of upper urinary tract urothelial carcinoma.
3. Hexylaminolaevulinate AND the diagnosis of upper tract urothelial cancer.
4. Blue-light diagnosis of upper tract TCC.
5. Fluorescence photo-detection of upper urinary tract TCC.
6. HexVix™ ureteroscopy (HexVix™ is the commonly used brand name of HAL).

The International Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov website were also searched for ongoing or recently completed trials. PROSPERO was searched for ongoing or recently completed systematic reviews. Conference proceedings of the British Association of Urological Surgeons, (BAUS), European Association of Urology (EAU) and the AUA for the previous two years (2013–2015) were included in the search. To further enhance the search yield, reference lists of the included studies and systematic reviews identified in the search process were scanned. Abstracts review was carried out initially. In case of any doubts about meeting the inclusion criteria, the full report was reviewed. If doubt still remained, the corresponding authors were directly contacted. All studies in the English language, as well as the studies that could be translated using Google translate, were included, with the exception of review articles. The present systematic review included all experimental studies relating to the PDD of UUTUC. All participants included were aged $\geq$18 years. The diagnostic test accuracy assessment tool and the meta-analysis included the eligible studies only.

The intention was to use the Cochrane risk of bias assessment tool for both randomised and non-randomised trials. However, the search did not identify any randomised trials. Therefore, the Cochrane Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) assessment tool was used [21]. For quality assessment of the studies included, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool was used [22].

The intervention being assessed was the systemic administration of a photosensitiser, usually 3–4 h before the procedure, in the form of 5ALA or the retrograde injection of HAL into the ureter and kidney intraoperatively. Direct comparison was carried out between the effectiveness of PDD as compared to white-light (WL)-URS, which is regarded as the current standard of care. As a part of one study the accuracy of CTU was compared to PDD [23].

Outcome measures

The diagnostic test accuracy in the form of sensitivity and specificity, as well as the extent of toxicity associated with the photosensitisers, were the primary outcome measures. Other outcome measures were, the number of individual cases diagnosed only by PDD, as well as the number of cases missed by PDD and that were detected by WL-URS or CTU.

Data collection and analysis

Data were collected using standard data extraction forms (included in Appendix 1). The main items of the extracted data were; demographic data (age, gender), patterns of clinical presentation, number of new cases diagnosed using PDD as opposed to recurrent or concomitant TCC or CIS, imaging method findings (e.g. CTU), type of photosensitiser used, and timing of administration. In addition to the above, the data collection forms extracted the reported efficacy of PDD either in the form of specificity and sensitivity or number of cases diagnosed based on PDD only. The toxicity associated with the photosensitisers was reviewed at the individual patient data level to assess the toxicity related outcome. Data extraction forms were completed independently by two different individuals.

The sensitivities and specificities were expressed as a numerical value with the 95% CI. The statistical significance for the heterogeneity and diagnostic accuracy were assessed. Any chi-squared $P \leq 0.05$ was considered to be statistically significant.

Results

In all, 17 studies were identified from the Medline, EMBASE, Google scholar, the CENTRAL trials registry of the Cochrane Collaboration and conference proceedings search. Two more studies were identified after screening the reference list of the initial search. After abstract and full text review, seven studies and one abstract were eligible for inclusion. Out of the seven studies, none was randomised, two were prospective and four were retrospective. Details of the included studies are shown in Fig. 1 [23–30], which depicts the Preferred Reporting Items for Systematic Reviews and

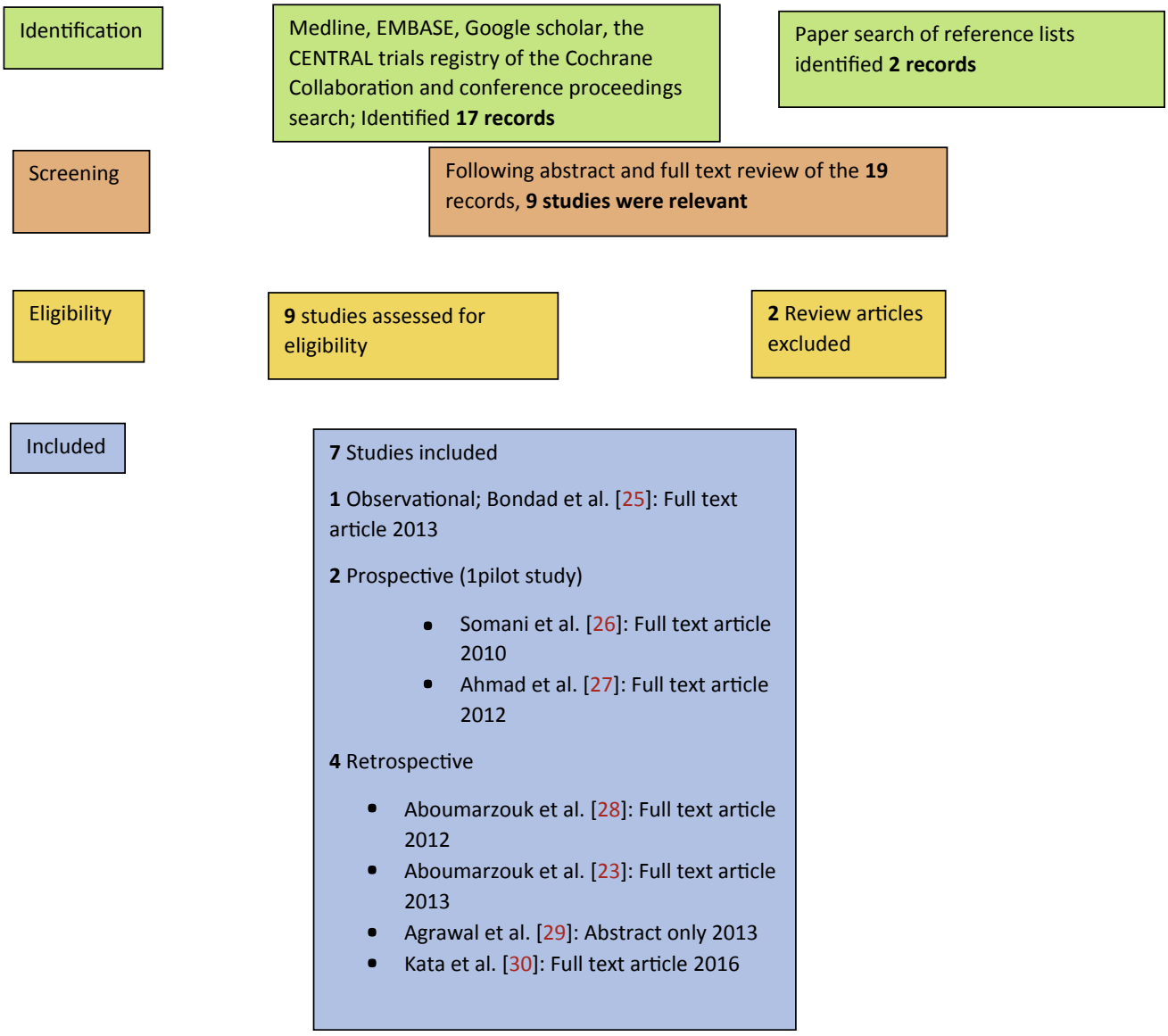

Fig. 1 PRISMA flow diagram for PDD in UUTUC [24].

Meta-Analyses (PRISMA) flow diagram. The total number of patients included was 194.

In general, the risk of bias of the included studies was moderate at its best level. Table 1 [23,25–30] with the table comments gives the details. Table 2 [23,25–30] shows the demographic data of the patients, as well as the quality assessment of the included studies as per the QUADAS-2 tool. The diagnostic accuracy of the PDD compared to conventional WL-URS, as well as CTU, was addressed in several studies as detailed in Table 3 [23,27–30]. Three studies expressed the diagnostic accuracy of PDD and WL-URS in numerical figures [23,28,30].

The overall adverse events' rate was 25.8% and the most common adverse event was hypotension. It was shown to cross the threshold for cerebral ischaemia in three patients, followed by light-sensitive facial skin rash and deranged liver enzymes, the respective percentages are shown in Fig. 2. All patients were treated symptomatically with satisfactory response with no long-term sequelae for up to 6 months.

Discussion

Upon reporting on the two main objectives of this review, the key findings for the diagnostic accuracy of PDD in UUTUC, as shown in the results section, revealed that PDD had better sensitivity in all the available studies. For specificity, PDD was better in two studies [28,30], while one study showed equal specificity at 100% for PDD and WL-URS [23].

One study [23] compared PDD to CTU, which is the imaging method of choice for diagnosing UUTUC. It favoured PDD to CTU in both sensitivity and speci-

Table 1 Assessment of risk of bias using the Cochrane tool for non-randomised studies.

Reference	Confounding bias	Selection bias	Bias in classification of intervention	Bias due to departures from intervention	Bias due to missing data	Bias in measurement of the outcome	Bias in selection of the reported results	Overall bias
Somani et al. [26]	Low	Serious	Low	Low	Low	Moderate	Low	Serious
Bondad et al. [25]	Moderate	Low	Low	Low	Low	Low	Low	Low to moderate
Aboumarzouk et al. [28]	Low	Moderate	Low	Low	Low	Low	Low	Low to moderate
Ahmad et al. [27]	Low	Low	Low	Low	Low	Low	Low	Low
Aboumarzouk et al. [23]	Low	Low	Low	Low	Low	Low	Low	Low
Agrawal et al. [29]	Low	Low	Low	Low	Low	Moderate	Low	Low to moderate
Kata et al. [30]	Low	Low	Low	Low	Low	Low	Low	Low

Overall risk of bias was judged as serious in the study of Somani et al. [26] as it included four patients only, implying the high likelihood of selection bias. Bondad et al. [25], assessed 5ALA associated hypotension. As some patients are taking essential anti-hypertensive medication already, this may exert some confounding. Agrawal et al. [29] and Ahmad et al. [27] did not report any diagnostic accuracy outcomes. With the exception of Aboumarzouk et al. [28], Aboumarzouk et al. [23] and Ahmad et al. [27], none of the other studies gave information about the conflict of interests.

ficity, with a statistically significant difference for specificity. The main advantage of PDD, as highlighted by Kata et al. [30], is in patients with flat carcinoma (CIS) or dysplasia, which is regarded as pre-malignant lesion. In fact, this seems to have mirrored the findings from studies on bladder PDD, which showed higher detection rates for CIS [32]. The toxicity associated with 5ALA, was reported in 25% of the total cohort of patients in the present study. These were all minor in nature and regarded as Clavien–Dindo grade I [33]. Hypotension was the leading complication constituting ~60% of cases. Close monitoring of blood pressure was highly recommended by Bondad et al. [25], whose study was designed mainly to assess 5ALA-associated hypotension. There were no reports on toxicity associated with HAL, which was administered by a ureteric catheter retrogradely in only one of the included studies.

In general, the quality of the included studies was low, as none of them were randomised. All the non-randomised cohort studies had their potential risk of bias, which were judged to be serious in some instances. The overall progression of the studies indicates that PDD in UUTUC is still in its early stages.

All included studies, specified a number of indications for performing PDD URS, e.g. in patients with normal conventional investigations (imaging and flexible cystoscopy) but persistent abnormal urinary cytology. These clinical scenarios usually represent a dilemma in new patients with suspected UUTUC. Other groups include unexplained hydronephrosis or indeterminate lesions on CTU. In the patients already diagnosed with UUTUC, some are conservatively managed with an endoscopic organ-sparing procedure, which requires regular surveillance and reflects the real need to establish a better role of PDD in UUTUC.

As per the European Medicines Agency, absolute contraindications to 5ALA include patients who are known to be hypersensitive to 5ALA or porphyrins, those who are diagnosed with porphyria or hepatic impairment, and pregnant women. Special precautions that need to be taken after administration include, avoiding exposure of eyes and skin to strong light sources (e.g. operating illumination, direct sunlight or brightly focused indoor light) for 24 h. Potentially phototoxic substances, such as Tetracyclines, Sulphonamides, Fluoroquinolones, and Hypericin extracts should be avoided, as well as potentially hepatotoxic substances. Extra caution needs to be taken in patients with pre-existing cardiovascular disease, due to the anticipated decrease in systolic and diastolic blood pressure, pulmonary artery systolic and diastolic pressure, as well as pulmonary vascular resistance. Upon comparing the currently used routes for administration of 5ALA, which are oral and intravesical, it is apparent that most of the studies in the present review used the oral form, as it is easier and more practical to assess the UUT. Inoue et al. [34] found no significant difference in diagnostic accuracy, ability for PDD, or recurrence-free survival between the oral and intravesical routes. All procedures were well tolerated by all patients without any severe adverse events. Nevertheless, that study was carried out in the setting of bladder cancer and not UUTUC, which is the main emphasis of the present review. Moreover, it was retrospective in nature. One prohibitive factor to the oral form is its cost.

Table 2 QUADAS-2 tool for the assessment of quality of diagnostic test accuracy.

Reference	Number of patients	Age, years, mean (SD) or range	Patient selection	Index test	Reference standard	Flow and timing	Applicability concerns		
							Patient selection	Index test	Reference standard
Somani et al. [26]	4	70–82	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bondad et al. [25]	24	71 (8.1)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Aboumarzouk et al. [28]	32	73.3 (6.5)					Low	Unclear	Low
Ahmad et al. 2012 [27]	26	70.3 (11)					Low	Unclear	Low
Aboumarzouk et al. [23]	30	70 (11)					Low	Low	Low
Agrawal et al. [29]	24	NM					Low	Unclear	Unclear
Kata et al. [30]	54	72.6 (9.5)					Low	Low	Low

() Low risk of bias () High risk of bias () Unclear.

N/A, not applicable; NM, not mentioned. The index test in all studies was flexible ureteroscopy after administration of a standard dose of 1.5 g oral 5ALA taken 3–4 h preoperatively, with the exception of Agrawal et al. [29] who used HAL instilled intra-renally with no specification of timing in relation to endoscopic inspection. White-light ureteroscopy was regarded as the reference test as it is the standard practice otherwise. There was a high risk of bias across all the studies with regards to timing of application of either PDD or white light as the ureteroscopes used allowed the simultaneous use of PDD and white light.

Table 3 Diagnostic accuracy of PDD, white light and CTU.

Author	Sens./specif. of PDD, %	NPV/PPV for PDD, %	Sens./specif. of WL, %	NPV/PPV of WL, %	Sens./specif. of CTU, %	NPV/PPV of CTU, %	Number detected only by PDD
Aboumarzouk et al. [28]	96/100	88/100	80/86	55/95	NI	NI	NI
Aboumarzouk et al. [23]	94/100	92.9/100	82/100	81/100	81/21	50/54	3
Ahmad et al. [27]	NI	NI	NI	NI	N/A	NI	10
Kata et al. [30]	95.8/96.6	96.6/95.8	53.5/95.2	75/88.5	N/A	N/A	NI
Agrawal et al. [29]	NI	NI	NI	N/A	NI	NI	5

NI, no information given; **NPV,** negative predictive value; **PPV,** positive predictive value; **Sens.,** sensitivity; **specif.,** specificity.

The widely employed technique for PDD URS was described by Kata et al. [35] in a review article about their single-centre experience. They described using a Tricam II SL PDD pendulum camera head (Karl Storz GmbH), as it allows the detection of the red light (spectrum between 600 and 700 nm). They enhanced the image brightness by adjusting the gain settings and reducing the frame rate from 1/50 in WL mode down to a variable 1/15 in blue-light mode. According to them, this allows each frame to be adequately exposed, as well as to provide the operator with an image bright enough for better visualisation. They used a fluid light cable (Karl Storz GmbH) to ensure adequate blue-light transmission, as the fluid cable blocks the residual infrared light. For flexible URS, PDD Flex-X2 (Karl Storz GmbH) was used. The eyepiece of the scope is fitted with a long-pass filter, which blocks light of <450 nm to reduce blue excitation light (diffusely backscattered by the tissue). They advocated visualising the intra-mural ureter with a semi-rigid ureteroscope before the negotiation of the PDD Flex-X2, for this purpose, a CE prototype removable long-pass eyepiece filter (Karl Storz GmbH) was used. This filter is placed between the camera and the eyepiece for non-PDD.

The initial part of the PDD technique as described by Kata et al. [35], involves a semi-rigid 7.5-F ureteroscopy

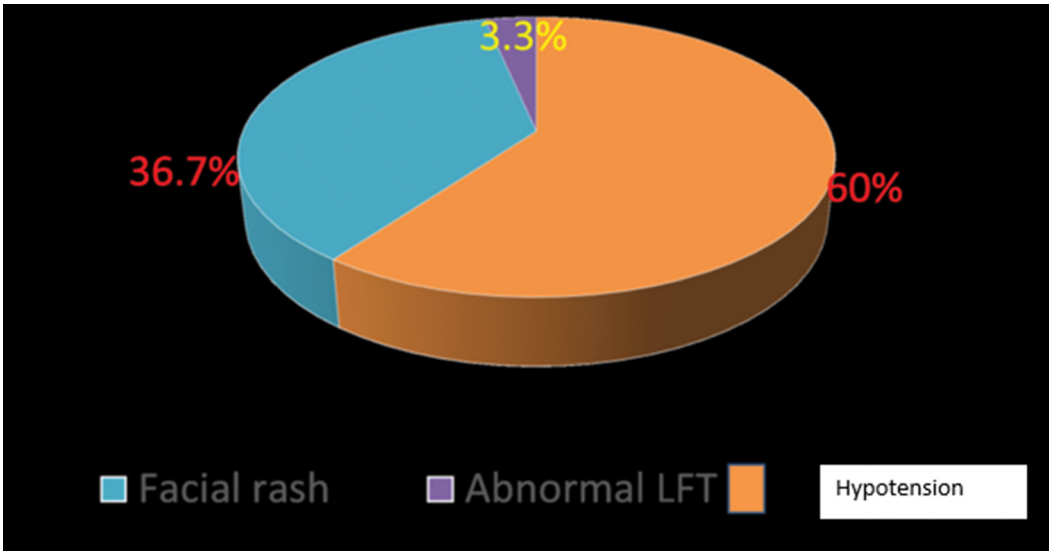

Fig. 2 Distribution of the adverse events associated with 5ALA.

over a guidewire up to the distal ureter only, followed by a (wireless) flexible PDD ureterorenoscope. The main reason of abandoning the use of the guidewire is to reduce the chances of bleeding that could disturb blue-light visualisation. Access sheath use was not recommended unless negotiation of the flexible ureterorenoscope was found to be difficult. Normal (0.9%) saline was used for irrigation. A barbotage sample was sent for cytology. The equipment allows simultaneous WL and blue-light inspection of the UUT. Kata et al. [30] described the urothelium of normal UUT to be blue during PDD URS, with the exception of the calyceal papillae, which may appear slightly red. If a suspected area was encountered, then the angle of inspection is changed to verify the fluorescence and exclude a tangential artefact before tissue sampling. For the technique of biopsy, they recommended opening the forceps at a distance to the UUT wall to avoid detaching urothelial cells, which could lead to a false-positive biopsy result, called 'denuding cystitis' or 'clinging CIS'.

As far as the technical shortcomings and pitfalls of PDD URS are concerned, the tangential effect described above was highlighted by Bus et al. [36] in a systematic review on the various optical technologies used in the UUT, as an inherent source of difficulty in the ureter due to the angle of the scope. Other sources of false positives are recent stenting and inflammatory conditions of the ureter. Furthermore, normal mucosa may sometimes retain some amount of the endogenous PPIX. Luckily enough, the phenomenon of photobleaching, during which chemical decomposition of PPIX takes place earlier than desired, does not happen in the ureter [37].

Evolution of the studies on UUT PDD

Somani et al. [26] reported the feasibility and safety of the procedure on only four patients. They set the concept of comparing PDD to the standard of care, i.e. WL-URS. Subsequently, Aboumarzouk et al. [28,23] reported on two consecutive cohorts of patients and reported more objective measures such as the sensitivity, specificity, negative predictive values. They described a standardised technique for performing the PDD URS. Moreover, they highlighted the distinctive ability of PDD to detect CIS and dysplasia compared to WL-URS. In a previous report, dysplasia was linked to CIS making it a worrisome finding that needs timely intervention [31].

In their first cohort, Aboumarzouk et al. [28] reported that PDD missed one high-grade (G3) tumour with no obvious explanation. In their subsequent study, Aboumarzouk et al. [23] included CTU in the comparison as mentioned above. They reported failure of PDD to detect one tumour that was detected by both WL-URS and CTU. The authors attributed this to the location of the tumour without giving the exact location. For 5ALA toxicity, they highlighted an important finding of increased risk of hypotension in patients who took their antihypertensive medication on the day of procedure, so they advised against taking antihypertensive medication on the morning of the procedure. They also suggested combining PDD with narrow-band imaging (NBI) technology to improve the diagnostic accuracy. NBI refers to the use of light at certain wavelengths, blue (415 nm) and green (540 nm), which are the most absorbed by haemoglobin. This allows better visualisation of highly vascular areas, such as malignant tissue. NBI could be more appealing than PDD, as it does not involve the use of a photosensitiser, which was regarded as a limiting factor to the wider application of PDD in a systematic review by Bus et al. in 2015 [36]. Currently, there are commercially available cystoscopes that provide a NBI wavelength with a push of a button. A study by Traxer et al. [37]

reported on 27 patients, 14 of whom were known cases of UUT-TCC as follow-up and 13 patients with first-suspicion of cancer. URS was performed using both WL and NBI. All suspicious areas were biopsied. They reported a subjective improvement of the endoscopic visualisation of the tumours, and a detailed description of the vascular architecture. Objectively, five additional tumours (14.2%) in four patients, as well the extended limits of three tumours (8.5%) in three patients were detected by NBI when findings by WL imaging were considered normal. A systematic review by Zheng et al. [38] included eight studies with a total of 1022 patients; they concluded that the diagnostic precision of NBI was superior to WL cystoscopy. One randomised trial showed the superiority of NBI vs WL cystoscopy in the setting of second-look transurethral resection of bladder tumour; however, it was retracted later due to a randomisation error [39]. The Storz Professional Imaging Enhancement System (SPIES), optical coherence tomography (OCT) and confocal laser endomicroscopy (CLE) are all new technologies in the field of optical enhancement during urinary tract endoscopy.

Ahmad et al. [27] combined PDD URS with WL cystoscopy in a cohort of patients with a mixture of UUT and bladder TCC. They reported the detection of 10 more lesions by PDD that were missed by both WL-URS and CTU, out of which seven were malignancies and two showed dysplasia. As part of their study limitations, they highlighted the subjective nature of perceiving fluorescence and recommended establishing a standardised grading system for fluorescence. This study quoted £110 as the cost of one vial of 5ALA (1.5 g) at that time.

In the largest study included in the present review, Kata et al. [30] inspected 106 UUT units and concluded better sensitivity for PDD, which was shown to be statistically significant for the first time. Again they reported the trend of a better ability of PDD to detect CIS and dysplasia.

Strengths and limitations

The present review is novel being the first to focus on the diagnostic accuracy and the overall adverse effects of PDD in UUTUC. The PRISMA standards were adhered to as much as possible. The results that emerged from the present review highlight the trend of PDD URS to detect CIS and dysplasia, both of which can potentially be treated conservatively, sparing patients the radical standard treatment of nephroureterectomy. This would be a key element in considering wider use of PDD.

The present study has several limitations. First, is the relatively small number of studies and patients, which in part is related to the overall prevalence of the disease. Secondly, the poor quality of the studies available to date is a real obstacle to strongly base any practice changes on the present review. A third limitation was the fact that a meta-analysis of the pooled diagnostic accuracy tests was considered to be inaccurate, as the eligible studies all came from the same institute with no raw data available. This would have made the review susceptible to duplication errors. However, the similarity in the methodology between these three studies may have been an advantage, due to the anticipated low chances of heterogeneity.

Future research suggestions

For PDD in UUTUC to become a recommended option, the way should be paved by multicentre randomised trials. This might require the international collaboration of different institutes, as the disease prevalence is quite variable with some regions, such as South East Asia and the Balkan regions, having more cases. The initial emphasis would be on establishing the diagnostic accuracy and detection advantage over the standard of care at the level of multicentre randomised trials. Further research on the optimum technique, especially standardisation of the perception of fluorescence intensity and its relation to the histological results, is also required. Ultimately, large studies with sufficient follow-up periods will help to establish the influence of PDD on recurrence and survival.

Conclusion

The present systematic review included seven studies of low-to-moderate quality, none of which was randomised. PDD of UUTUC was found to have promising early results. The largest available published study, reported statistically significantly better sensitivity of PDD compared to WL-URS. For specificity, PDD was better than both WL-URS and CTU, and this was statistically significant when compared to CTU. Compared to CTU, PDD has a better sensitivity but this was not statically significant. PDD showed the distinct advantage of detecting more CIS and dysplasia. The toxicity associated with 5ALA is minor in nature, with no long-term adverse effects within the time-frame of the studies included. Hypotension is the most common adverse effect; therefore, pausing anti-hypertensive medication and continuous monitoring of blood pressure are essential.

Conflicts of interest

None.

Source of funding

None.

Appendix A.

Data extraction form

1. Study type;
2. Number of participants/procedures
3. Study Demographics
   Age range: Gender: Others:
4. Number of new patients
5. Mode of clinical presentation
6. Number of previously known patients
   Known bladder TCC Known upper tract TCC
7. Imaging modality used and findings
8. cytology results
9. Type of Photosensitizer
   Dose Timing in relation to procedure
10. Procedure details
11. Histopathology
12. Reported sensitivity and specificity
13. Photosensitizer related toxicity

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