Photodiagnosis and Photodynamic Therapy 13 (2016) 255–260

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Photodynamic diagnostic ureterorenoscopy: A valuable tool in the detection of upper urinary tract tumour

Slawomir G. Kata[a,b,*], Omar M. Aboumarzouk[a,c,d], Abdullah Zreik[e], Bhaskar Somani[a,f], Sarfraz Ahmad[a], Ghulam Nabi[a,g], Ronald Buist[b], Carol Goodman[b], Piotr Chlosta[h], Tomasz Golabek[h], Harry Moseley[b,i]

[a] Department of Urology, Ninewells Hospital and Medical School, Dundee, UK
[b] The Scottish Photodynamic Therapy Centre, Ninewells Hospital & Medical School, Dundee, UK
[c] Department of Urology, Royal Gwent Hospital, Newport, Wales, UK
[d] Islamic Universities of Gaza, College of Medicine, Gaza, Palestine
[e] Department of Urology, Gartnavel General Hospital, Glasgow, UK
[f] University Hospitals Southampton NHS Trust, Southampton, UK
[g] Division of Imaging and Technology, University of Dundee, Ninewells Hospital & Medical School, Dundee, UK
[h] Academic Urological Unit, Collegium Medicum, Jagiellonski University, Krakow, Poland
[i] The Photobiology Unit, University of Dundee, Ninewells Hospital & Medical School, Dundee, UK

ARTICLE INFO

Article history:
Received 7 May 2015
Received in revised form 31 July 2015
Accepted 4 August 2015
Available online 6 August 2015

Keywords:
5-Aminolevulinic acid
Cystoscopy
Haematuria
Photodynamic diagnosis
Ureterorenoscopy
Upper urinary tract tumour

ABSTRACT

Background: Photodynamic diagnosis increases the detection rate and hence decreases recurrence rates of urothelial cancer (UC) of the bladder. This technique has been implemented in the upper urinary tract and like in the bladder, has shown to increase the detection rate of urothelial lesions.
Objectives: To determine the sensitivity, specificity, and detection rates for photodynamic diagnostic flexible ureterorenoscopy (PDD-FURS) and white light ureterorenoscopy (WL-FURS).

Design between 2009 and 2013, PDD-FURS was performed within 106 Upper urinary tract (UUT) Units (Mean age—72.6 ± 9.5). Indications for the procedure included abnormal upper urinary tract on imaging, normal flexible cystoscopy with abnormal urine cytology, endoscopic treatment and follow-up of UUT UC. Oral 5-aminolevulinic acid was used as the photosensitizer administered 3-4 h pre-operatively.
Results: 48 lesions were detected, of which 95.8% (46/48) where visualised by PDD-FURS compared to 47.9% (23/48) shown by WL-FURS ($P < 0.0001$). PDD-FURS detected significantly more carcinoma in situ (CIS) or dysplasia lesions than WL-FURS (93.75% (15/16) vs. 18.75% (3/16), respectively, ($P = 0.0006$)). Furthermore, PDD-FURS detected significantly more UC lesions than WL-FURS (96.9% (31/32) vs. 62.5% (20/32) ($P = 0.007$)).

PDD-FURS was more sensitive (95.8; range: 85.7–99.5) than WL-FURS (53.5; range: 37.7–68.8) in detecting UUT-UC ($P < 0.0001$). There was no difference ($P = 0.716$) in the specificity between PDD-FURS (96.6; range: 88.1–99.6) and WL-FURS (95.2; range: 86.7–99).
Conclusions: Our results PDD-FURS with oral 5-ALA as photosensitizer suggest higher sensitivity and detection rate of urothelial tumours than WL-FURS, with a good safety profile. In our series, PDD-FURS enhanced the visualisation of flat lesions, such as CIS and dysplasia that otherwise would have been missed.

1. Introduction

Urothelial cancer (UC) of the upper urinary tract (UUT), including renal pelvicalyceal system and ureter, accounts for approximately 10% of all renal tumours and 5% of urothelial tumours [1–3]. The majority of cases are diagnosed during investigations of haematuria.

Radical nephroureterectomy with excision of a bladder cuff is the gold standard treatment of UUT-UC [4]. A more conservative approach may be adopted in patients with small, superficial, solitary, low grade disease or those unfit for radical treatment. Endoscopic treatment of low grade UUT-UC has emerged due to the advances of flexible ureterorenoscopes (FURS) combined with

* Corresponding author at: Department of Urology, Ninewells Hospital and Medical School, Urology Office, Ward 31, Dundee DD1 9SY, UK.
E-mail address: g.kata@nhs.net (S.G. Kata).

http://dx.doi.org/10.1016/j.pdpdt.2015.08.002
1572-1000/

modern laser and diathermy ablation technology [5,6]. However, there is a high recurrence rate for endoscopically managed UUT-UC (>50%), with 9% metastatic progression rate, and a 5-year recurrence free survival between 13 and 54% [7]. Therefore, endoscopic surveillance depends on regular ureterorenoscopy with periodic diagnostic imaging allowing for early detection and treatment of recurrences [5,8]. Nonetheless, the failure rate is almost 24% [7].

Photodynamic diagnosis (PDD) has been taken into the spotlight on terms of improvement of the UC recurrence rate. Blue light (BL) cystoscopy increases bladder tumours detection and facilitates a more complete resection, hence, increases recurrence free interval compared to white light (WL) alone [9]. The PDD-guided detection of CIS appeared to be superior to WL cystoscopy [10]. The PDD showed 23% additional CIS cases on initial investigations and 78% on follow up when compared to WL endoscopy [9]. Implementing PDD ureterorenoscopy (PDD-FURS) in the management of patients with the UUT lesions, we have echoed the results of its use in the bladder and found an increased detection rate of UUT lesions thereby allowing a more complete ablation [8,11]

The principle of PDD is based on the interaction between light and a fluorophore within the tissue. The flurophore, such as Protoporphyrin IX (induced by 5-aminolevulinic acid 5-ALA as photosensitizer) absorbs the light then re-emits it at longer wave length which is easily detected [9,12].

Our initial series of 32 patients, reported a high detection rate, sensitivity and specificity for PDD-FURS in detecting UUT lesions (96%, 96% and 100% respectively) [8]. We now present our complete cohort of patients comparing the diagnostic accuracy of PDD-FURS to that of WL-FURS using oral 5-ALA as the photosensitizer.

2. Material and methods

Between July 2009 and June 2013, all patients in Ninewells Hospital (single centre series) who met the recommended criteria of endoscopic management under regular surveillance for UUT-lesions, or had an abnormal UUT CT-Urogram finding, or normal flexible cystoscopy with abnormal urine cytology, or persistent visible haematuria despite negative investigations or unexplained hydronephrosis were included to undergo WL FURS followed by PDD FURS.

PDD was used in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice and the Declaration of Helsinki (2004), and was approved by our institutional 'Improvement and Quality Committee'. Patient demographics and outcomes were prospectively maintained on a secured database. Caldicott approval was granted and the lead consultant (SGK) is registered with the National Information Commissioner's Office.

Each patient received 1.5 g of oral 5-ALA dissolved in 50 ml of water (fruit juice added for flavour), 3–4 h before PDD FURS. The average time from taking the oral 5-ALA to the procedure was 262.3 ± 79.2 min (115–480 min).

All PDD-FURSs were performed or directly supervised by an experienced endourologist well versed with the use of PDD technique. The equipment used was the PDD-FlexX2 ureterorenoscope with a special fluorescence excitation light source (D-light-C, Karl Storz GmbH & Co., KG, Tuttlingen, Germany) with a protoporphyrin IX excitation filter permitting the blue-violet light (380–430 nm). For the semi-rigid ureteroscopy, a CE prototype removable long-pass eyepiece filter was used.

Each procedure was started with systematic documentation of findings on WL and BL inspection of the lower urinary tract followed by inspection of the UUT. All suspicious areas were biopsied and sent for histopathological examination separately. Biopsies were taken from small lesions first to prevent photobleaching effect. In case of normal appearance of the ureter, mapping biopsies (at least one from the proximal, middle and distal) were taken. Random quadrant biopsies were also taken from normal bladder (high risk group). Exophytic lesions in the UUT were sampled with a basket device. Biopsy findings were reported by an experienced pathologist.

Any patients with previously inserted ureteric stent had this removed 4 weeks prior to PDD-FURS, as stents can potentially induce an inflammatory process giving false positive fluorescence [13].

If the intramular segment of the ureter was not in favour of wireless negotiation of flexible ureterorenoscope, semirigid 4.5 F or 7.5 F ureteroscope was negotiated over a wire-guide (introduced into distal ureter only) to open the intramular segment of the ureter for easier access. Semirigid ureteroscope was withheld after being passed into the distal ureter, the guide wire was withdrawn and a flexible ureterorenoscope was negotiated into the ureter. Although trauma from the guide wire does not give any false positive fluorescence within the UUT, bleeding can disturb visualisation under blue light. Therefore, Grasso's wireless technique was followed [14]. Although a ureteric access sheath is shown to be safe in the management of UUT-UCC [15], we did not use it routinely for diagnostic ureterorenoscopy unless navigation of flexible ureterorenoscope was difficult [16].

All abnormal lesions within the UUT suitable for endoscopic management were ablated with Holmium-YAG laser and diathermy probe. We did not insert a stent following diagnostic ureterorenoscopy with the exception of solitary kidney. Our follow-up included initial ureterorenoscopy three months after the primary treatment. If no recurrence was detected, follow-up ureterorenoscopy was done six monthly for 2 years and annually thereafter for 5 years. CT Urogram (and CXR) was performed annually.

The statistical analysis was conducted at procedure level and consisted of analysis of the visualisation of the lesion(s) under either BL or WL and correlation with the histological results of biopsies leading to diagnostic accuracy values: true positive (TP), true negative (TN), false positive (FP), and false negative (FN). Normal appearance of the UUT unit under WL and BL in low risk patients who did not develop any recurrences during follow-up was considered as TN with no biopsies taken. The variables led to the calculation of the sensitivity, specificity, negative and positive predictive values (NPV and PPV), and accuracy for the correct detection of the lesion for PDD-FURS and WL-FURS.

A comparative analysis was conducted between PDD-FURS and WL-FURS results using a chi-square analysis. P values <0.05 were considered significant. Analysis was done using the meta-analysis of diagnostic and screening tests 1.4 programme (Unidad de Bioestadistica Clinica, Hospital Ramon y Cajal, Madrid) and Review Manager 5.1.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

3. Results

A total of 106 UUT-units were inspected. Table 1 presents the patients' demographics and Table 2 gives indications for ureterorenoscopic investigation. Of the 106, 48 UUT-units were found to have lesions on endoscopic inspection. Nearly half of which (48%, 23/48) were in the surveillance group, while the remaining lesions were found during initial investigations for their respective indications. Majority of these patients had pathologically confirmed UC ($n = 32$), with 11 patients having CIS/dysplasia, and 5 patients having both pathological lesions with a predominance of CIS/dysplasia (Photos 1–3).

Three quarter (15/20) of the ex-smokers were found to have lesions, while 87.5% (14/16) of the current smokers and 50% (9/18)