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Photodynamic Diagnosis for Upper Urinary Tract Urothelial Cell Carcinomas

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Upper urinary tract urothelial cell carcinomas (UUT-UCCs), account for 5% of all urothelial tumours with transitional cell carcinoma being the most common type [1,2]. Sixty percent UUT-UCCs are invasive at diagnosis thus reflected by poor outcomes [3,4]. Multidetector computed tomographic urography (MDCTU) is currently considered as the gold standard for the investigation of UUT-UCCs [5,6]. For polypoid lesions between 5 and 10 mm the detection rate with MDCTU are fairly accurate with 96% sensitivity and 99% specificity. However, sensitivity drops to 89% for lesions <5 mm and to 40% for <3 mm lesions [7,8]. These small lesions represent either non-invasive superficial tumours or carcinoma *in situ* (CIS) [9]. Endoscopy assessment especially with flexible ureterorenoscopy (FURS), can explore the ureter macroscopically and reach renal cavities in 95% of cases, obtain biopsy and determine tumour grade in 90% of cases with a low false-negative rate [10].

Traditionally, the standard treatment for UUT-UCCs is a radical nephroureterectomy and a bladder cuff removal [2,11]. However, in selected patients, conservative endoscopic ablation with LASER is explored recently and has produced comparable results to that of radical surgery [2,12]. The endoscopic ablation necessitates repeated FURS and depends on accurate localization of malignant lesions [2,11]. However, even direct visualization with conventional white light FURS can miss small flat tumours [2].

The role of Photodynamic diagnosis (PDD) is now well established in the management of bladder tumours, especially for flat tumours and carcinoma *in situ* (CIS) [13-15]. For photosensitization, two pharmacological agents, Hexaminolevulinate and 5- Aminolevulinic Acid (5-ALA), have been investigated for bladder tumours [16-20].

Application of PDD for UUT-UCCs is relatively a new exciting innovation. For UUT-UCCs photosensitization of the upper urinary tract urothelium depends on systemic administration of the photodynamic pharmacological agents. One of these agent, 5 - ALA, has been investigated recently and showed promising results in detection of UUT-UCCs [21].

PDD uses fluorescence to localize malignant lesions by selective accumulation of Protoporphyrin IX in the tumour tissues. PDD principle is based on the interaction of a photosensitizing agent such as 5 - ALA, that has a high uptake by tumour cells, and light (photon) with an appropriate wavelength [2,13,14]. The agent absorbs light as high energy per photon and re-emits it with a lower energy per photon, producing a different wavelength [2,13,14], hence enhancing visualization under blue light.

The role of blue light assisted FURS for investigating UUT- UCCs is still in early stages [22]. Few reported series, using 5 - ALA, have shown enhanced detection of UUT-UCCs with PDD [21,23,24]. The sensitivity and specificity of PDD to detect abnormal tissues in upper urinary tract was reported 96% and 100%, respectively [21]. Furthermore, PDD was able to detect more tumours including CIS than with white light alone [21]. In addition to the detection of overt malignant urothelial lesions, urothelial dysplasia also showed higher fluorescence [24]. Appropriate management and prediction of prognosis of the urothelial cancers require a careful endoscopic evaluation of whole urinary tract. PDD for upper tract also allow bladder inspection under blue light and showed to detect concomitant bladder cancers [24]. Although the PDD for UUT-UCCs is promising but not without side effects, mainly hypotension and facial redness [21,24].

Early diagnosis and detection of occult urothelial lesions is important as these have important implications on disease progression and management decisions. PDD for upper tract is a step forward in enhancing diagnostic accuracy of FURS. Initial result of PDD for UUT-UCCs are quite encouraging showing feasibility and safety of PDD with additional advantages of detecting lesions not visualised with conventional white light endoscopy. This will be more valuable in patients selected for conservative endoscopic ablation of UUT-UCCs, as PDD will allow complete treatment and subsequent reduction in recurrence. Current evidence support potential use of PDD for investigating, treating and for follow up of patients with UUT-UCCs. However, the available data is quite limited, further multicentre trials with a larger cohort of patients are required to evaluate PDD safety and benefits. Additionally, due to lack of long-term follow up in reported series, correlation of PDD of UUT-UCCs with recurrence free and overall survival need to be established.

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