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REVIEW

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

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KEYWORDS

Upper tract TCC;
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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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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