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Collaborative Review – Bladder Cancer

Photodynamic Diagnosis in Non–Muscle-Invasive Bladder Cancer: A Systematic Review and Cumulative Analysis of Prospective Studies

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Abstract

Context: The clinical benefit of photodynamic diagnosis (PDD) with 5-aminolevulinic acid or hexaminolevulinate in addition to white-light cystoscopy (WLC) in bladder cancer has been discussed controversially.

Objective: To assess in a systematic review the effect of PDD in addition to WLC on (1) the diagnosis and (2) the therapeutic outcome of primary or recurrent non–muscle-invasive bladder cancer investigated by cystoscopy or transurethral resection.

Evidence acquisition: An electronic database search of Medline, Embase, the Cochrane Library, and CancerLit was undertaken, plus hand searching of relevant congress abstracts and urologic journals. Trials were included if they prospectively compared WLC with PDD in bladder cancer. The review process followed the guidelines of the Cochrane Collaboration. Two reviewers evaluated independently both trial eligibility and methodological quality and data extraction.

Evidence synthesis: The primary end point of diagnostic accuracy was additional detection rate. The primary end points of therapeutic outcome were residual tumour at second resection and recurrence-free survival (RFS). Seventeen trials were identified. Twelve diagnostic trials used WLC and PDD with the same patients. Seven reported results for the subgroup of patients with carcinoma in situ (CIS). Five randomised trials studied therapeutic outcome. The results were combined in random effects meta-analyses if end points, designs, and populations were comparable. Twenty percent (95% confidence interval [CI], 8–35) more tumour-positive patients were detected with PDD in all patients with non–muscle-invasive tumours and 39% (CI, 23–57) more when only CIS was analysed. Heterogeneity was present among diagnostic studies even when the subgroup of patients with CIS was investigated. Residual tumour was significantly less often found after PDD (odds ratio: 0.28; 95% CI, 0.15–0.52; $p < 0.0001$). RFS was higher at 12 and 24 mo in the PDD groups than in the WLC-only groups. The combined p value of log-rank tests of RFS was statistically significant (0.00002).

Conclusions: PDD detects more bladder tumour–positive patients, especially more with CIS, than WLC. More patients have a complete resection and a longer RFS when diagnosed with PDD.

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1. Introduction

Bladder cancers are the second most common urologic malignancy in the Western world, with an estimated 70 980 new cases diagnosed each year in the United States [1] and 85 880 in Europe [2]. Seventy to 80% of patients have a non–muscle-invasive bladder cancer (NMIBC; eg, confined to the mucosa, Ta, T1, carcinoma in situ [CIS], according to the 2002 TNM classification). The mainstay of treatment for NMIBC has always been complete transurethral resection (TUR), first control cystoscopy after 3 mo, and further cystoscopic follow-up surveillance. The probabilities of recurrence and progression for TaT1 bladder cancer at 1 yr range from 15% to 61% and from <1% to 17%, respectively. At 5 yr, the probabilities of recurrence and progression range from 31% to 78% and from <1% to 45% [3]. Consequently, as an adjunct to tumour resection, intravesical chemotherapy or intravesical immunotherapy is routinely used to reduce tumour recurrence rates and possibly delay or inhibit tumour progression to muscle-invasive disease.

It has been estimated that 10–20% of bladder tumours are overlooked in conventional white-light cystoscopy (WLC) [4]. One attempt at an improvement is urine cytology, but it lacks the immediate result warranted during TUR. Even 30 yr ago, physicians were advocating the use of photosensitising drugs for an optimised diagnosis and the treatment of bladder cancer. The method is based on the preferential accumulation of a photosensitising compound in neoplastic cells that emits a fluorescence in the red part of the spectrum under blue-violet excitation or illumination, enabling visualisation of the tumour. The first prodrug to be administered topically for photodynamic diagnosis was 5-aminolevulinic acid (5-ALA). The small molecule itself has no photochemical activity. The transient formation of endogenous photoactive porphyrins is induced by 5-ALA [5]. Hexylaminolaevulinic acid (HAL), an ester derivative of 5-ALA, has a better bioavailability that reinforces the selective tissue accumulation of photoactive porphyrins, the essential condition of the value of photodynamic diagnosis (PDD) added to WLC.

Patients do not receive the correct early treatment when high-grade flat lesions are not detected completely, and this has a decisive impact on therapeutic outcome. In addition, the incomplete resection of papillary tumours results in a so-called recurrence that is merely previously undetected tumour.

Clinical trials of phases 1–3 led to the approval of HAL (Hexvix) for the detection of bladder cancer in 26 European countries. According to the 2008 European Association of Urology (EAU) guidelines, "PDD is more sensitive than conventional procedures in detecting malignant tumour and the benefit for recurrence-free survival (RFS) was shown in several small randomised clinical trials."

Numerous clinical trials of phases 2–4 have been performed until recently with heterogeneous results [6]. The aim of the current systematic review was to evaluate the effect of additional PDD on (1) the diagnostic accuracy of cystoscopy and (2) the therapeutic outcome. Tumour entity (Ta, T1, CIS) is considered a source of the heterogeneity of results.

2. Evidence acquisition

2.1. Criteria

Aiming at the hardest evidence, just two types of prospective studies were considered. Diagnostic accuracy was investigated by applying PDD additionally after WLC in the same patients using histology of biopsies taken at the detected locations as the reference standard. Therapeutic outcome was assessed after randomising patients undergoing TUR to either white light (WL) alone or combined with PDD. Patients had to have suspected or proven NMIBC. Both procedures were considered in primary and recurrent tumours. The primary end point for the studies of diagnostic accuracy was an additional detection rate, that is, the proportion of patients additionally and correctly identified by PDD to have bladder cancer. This would be the increase in sensitivity if the histologic findings would cover residual lesions as well. A patient-based measure was preferred over a lesion-based one for clinical relevance. Less important in the treatment regimen is our secondary measure of diagnostic accuracy, additional false-positive rate, that is, the proportion of additional false positives produced by PDD. The primary end points of therapeutic outcome in randomised trials were residual tumour at second resection and RFS.

2.2. Search

An electronic database search of Medline, Embase, the Cochrane Library, CancerLit, and ClinicalTrials.gov was undertaken in January 2009. The proceedings of the American Society of Clinical Oncology, the American Urological Association, the EAU, Deutsche Gesellschaft für Urologie, and the journals *European Urology* and *Journal of Urology* were manually searched for clinical trials and review articles (1990–2008) in English, German, or French that compared WL TUR or cystoscopy alone with TUR or cystoscopy plus PDD. Appendix A lists the detailed search strategies.

We asked authors of the selected studies to supply results on the primary end points of this review if their articles reported only related end points. Authors and experts in the field were asked for additional studies.

2.3. Data extraction and analysis

The review process was performed according to the guidelines of the Cochrane Collaboration [7]. Two reviewers (IK and MS) performed the database searches and application of the selection criteria independently and were followed by a consensus reading based on the two resulting lists combined. Quality of selected reports was assessed by a questionnaire compiled from items of the Consolidated Standards of Reporting Trials (CONSORT) [8] and the Standards for Reporting of Diagnostic Accuracy (STARD)