Photodynamic Diagnosis in Non-Muscle-Invasive Bladder Cancer

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Abstract

Objective: This paper reviews the development and clinical validation of photodynamic diagnosis (PDD) of bladder cancer.

Methods: The authors reviewed the literature on the development of PDD, in particular the evidence for the clinical efficacy of hexaminolevulinate PDD in the diagnosis of bladder cancer.

Results: After initial work on ultraviolet cystoscopy following oral tetracycline, the focus of PDD research shifted to the use of synthetic porphyrins. First, the prodrug delta-aminolevulinic acid (ALA) was shown to cause a transient but significant accumulation of protoporphyrin IX (PpIX) in malignant or premalignant bladder tissue. Excitation by blue light leads to PpIX fluorescence (red), which distinguishes tumour from normal tissue (blue). Hexaminolevulinate (HAL, Hexvix), an ester of ALA, was then developed and has greater bioavailability and stability than the parent compound. It has been approved for clinical use in the diagnosis of bladder cancer. Clinical studies have shown that HAL PDD detects tumours, including carcinoma in situ (CIS), that are missed by conventional white-light cystoscopy.

Conclusions: HAL PDD is a valuable aid to the detection of bladder tumours, including CIS.

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1. Introduction

One of the aims of research into noninvasive bladder cancer is to identify biomarkers that will assist in tumour identification/characterisation and prediction of recurrence and progression [1]. However, no prognostic marker has yet been validated for routine clinical use, so disease assessment is still based mainly on clinical parameters, such as tumour size and aspect, multifocality, presence/absence of urothelial flat abnormalities, residual tumour following transurethral resection, and recurrence rate [2,3]. Photodynamic diagnosis (PDD, also known as fluorescence cystoscopy), used in addition to conventional cystoscopy, is a sensitive aid in the identification of bladder cancer. This article reviews the development of PDD and its clinical validation.
2. Conventional clinical assessment of noninvasive bladder cancer

Although PDD is recommended for the detection of carcinoma in situ (CIS) by the 2006 European Association of Urology (EAU) guidelines [4], the technique has not yet been introduced into routine urology. Use of conventional white-light cystoscopy and voided/bladder-wash cytology remains the standard of care for initial assessment and follow-up of bladder cancer.

The quality of visualisation obtained with white-light cystoscopy facilitates recognition of exophytic tumours, such as sessile or pediculated papillary tumours, but flat cancers, such as CIS and/or dysplasia with minimal/absent or unspecific urothelial abnormalities can escape detection [4]. The diagnostic success of cytology alone, that is, when not associated with labelling techniques such as Immunocyt or fluorescent in situ hybridisation (FISH) [5,6], relies mainly on the aggressiveness of the bladder cancer. The sensitivity and specificity rates for cytology are >80% with high-grade multifocal disease and/or diffuse CIS [7]. However, in low-grade disease, with no detectable exfoliated cells or with cells that display no clear-cut morphological criteria of malignancy, the sensitivity of cytology can fall to 50% or even less [7]. Before the development of PDD, detection of concomitant CIS required microscopic examination of several consecutive urinary samples [8].

Up to 83% of patients with CIS will develop invasive bladder cancer [9], so treatment decisions need to be based on optimal inspection of the bladder wall, using a method that addresses the following questions:

- Does the finding of a solitary papillary tumour exclude the presence of CIS or dysplasia?
- What is the real extent of mucosal alteration in the presence of multifocal disease?
- How should positive cytology be interpreted in the absence of a specific mucosal lesion?

These questions remain mostly unanswered by routine cystoscopy plus cytology.

3. Photodynamic diagnosis

3.1. The basic principles

PDD enhances the visual contrast between benign and malignant tissue by inducing a photodynamic process, resulting in selective emission of fluorescence from cancer cells.

Bladder tissue can be photosensitised by instillation of delta-aminolevulinic acid (ALA) or its derivative, hexamethyl(4-aminonitrile) (HAL, Hexvix). These agents are prodrugs; they lack photochemical activity themselves, but they initiate a series of biochemical reactions that result in a transient though significant accumulation of protoporphyrin IX (PpIX) or photoactive porphyrins (PAPs). Because of cellular enzymatic abnormalities in tumour tissue, PpIX/PAPs accumulate preferentially in malignant and precancerous tissue rather than in benign cells. When the bladder wall is illuminated (and excited) by blue light (~380–470 nm), the PpIX/PAPs entrapped in cancer cells emit red fluorescence (~693 nm), whereas normal bladder wall tissue appears blue-green. The different appearances of malignant and normal tissues can be monitored by an imaging device or observed directly by the naked eye through appropriate handling of the endoscopic instrumentation [10]. Furthermore, because ALA and HAL are topically administered via bladder instillation, the risk of a systemic reaction is very unlikely.

3.2. How photodynamic diagnosis was developed

Various methods for targeting tumours with a dye or photosensitizing agent during cystoscopy have been investigated over the past 40 yr.

In the early 1960s, researchers demonstrated that ultraviolet cystoscopy after oral tetracycline administration was a simple and practical technique that might be useful in the recognition of malignant areas not visible with standard white-light cystoscopy. However, several problems remained:

- The clinical trials lacked detailed information on methodology; for example, false positives were reported, but not false negatives.
- Oral ingestion of tetracycline pills for 4 consecutive days was likely considered unpleasant for patients.
- Tumours showed a nonhomogeneous and unspecific fluorescence; benign papilloma (now considered a papillary urothelial neoplasm of low malignant potential) and low-grade papillary urothelial carcinoma did not fluoresce [11,12].

Exogenous synthetic porphyrins—haematoporphyrin derivatives (HpDs) or dihaematoporphyrin ethers and esters—have been extensively used in photodynamic therapy for bladder cancer since 1975 [13]. The HpD Photofrin, used at a low intravenous
dose optimised to avoid systemic and skin photosensitisation, was reported to be a potential diagnostic marker in a small group of patients [14]. However, Photofrin tumour fluorescence was weak and required a complicated fluorescence diagnostic system based on a Krypton ion laser [15].

Porphyrin-based procedures were eventually simplified with bladder cancer endogenous photosensitisation by ALA, and later HAL [16,17]. After Kennedy et al demonstrated the clinical suitability of ALA [16], PpIX fluorescence induced by topical application of ALA was shown to be successful in the photodetection of early-stage neoplastic urothelial lesions [18–20]. However, ALA is a hydrophilic compound and cannot therefore penetrate all tissue, resulting in some clinical limitations, such as a long dwelling time and a variable PpIX fluorescence intensity and distribution [17]. HAL is an ester of ALA. It is more soluble and has a higher PAP formation capacity at a lower dose and stability [17], allowing a significantly shorter incubation time with a demonstrated improvement of PAPs tissue fluorescence homogeneity and distribution (Fig. 1) [21].

This increase in fluorescence obtained with HAL can lead to shorter integration times for the fluorescence images, compared to those obtained with ALA and, under certain conditions, to less streaking of the images.

3.3. Clinical studies of hexaminolevulinate photodynamic diagnosis

Initial clinical studies of HAL PDD confirmed the preclinical findings and raised the possibility of shortening the bladder instillation time to 1–2 h [17,22].

The first study of the sensitivity and specificity of HAL PDD [22] was published in 2003, based on findings in 52 patients with superficial bladder cancer who had received no topical therapy in the previous 3 mo, and who had no gross haematuria, porphyria, or allergy to HAL. An instillation of 50 mg of HAL was given 1 h before cystoscopy and transurethral resection of the bladder (TURB) using the Storz D-light system, which allows both white-light and blue-light bladder inspection. The surgeon undertook bladder mapping under white light, then switched to blue light. Every suspicious area was noted and resected, and all the biopsies were sent to one centre for pathology. A total of 143 histologically verified tumours were found in 45/52 patients. Tumours were detected in 43 patients by HAL PDD (Fig. 2) and in 33 patients by white-light cystoscopy. Ten patients in whom no tumour was detected with white light went on to have CIS detected by HAL (Fig. 3). Eleven of the exophytic tumours were detected only by HAL cystoscopy, including four T1 tumours in three patients. Overall, of 112 tumours detected during the procedure, 47 were detected by HAL PDD alone, and 4 were detected by white-light cystoscopy alone.

Comparing HAL PDD with white-light cystoscopy, the multicentre investigators report that the sensitivity of the methods is 96% versus 73%, respectively; the detection rate is 76% (108/143) versus 46% (65/140); and the specificity is 79% (221/278) versus 93% (255/274). In conclusion, the investigators state not only that the bladder tumour detection rate is higher

Fig. 1 – Hexaminolevulinate (HAL) fluorescence cystoscopy in a 50-yr-old female patient. The photoactive porphyrins (PAPs) are homogeneously distributed within the whole papillary tumour (pTa G1).

Fig. 2 – A T1G3 tumour nicely demarcated by hexaminolevulinate (HAL) fluorescence cystoscopy in a 76-yr-old patient.
with HAL PDD than with white-light cystoscopy, but that HAL PDD also improves the detection of CIS alone or associated with exophytic tumours—an important prognostic factor in bladder cancer.

The preliminary results of this initial study were confirmed by a larger European trial (PCB301/01) involving 286 patients at 19 centres [23]. The primary objective was to determine the proportion of patients in whom additional CIS lesions were detected when HAL PDD was used compared with white-light cystoscopy alone. As in the previous study, a within-patient design was adopted, with examination under white light first, then blue light, again with the Storz D-light system. All the detected lesions were mapped on a bladder chart, then resected and sent for a central, blinded pathology review.

Of the 286 patients recruited, 279 received HAL and were included in the safety analysis; 9 were subsequently excluded because of protocol violations, and 59 were used as training cases, leaving 211 available for assessment in the trial. Pathology confirmed that 17 of the 211 had no tumour and 83 had CIS (39%); 80 of the patients with CIS lesions were identified with HAL PDD (96%) and 64 with white light (77%); 18 patients had CIS only, and 33% of these were missed by white-light cystoscopy but detected by HAL PDD. Overall, HAL PDD detected 97% of all lesions, compared with 78% for white light; for CIS, the respective detection rates were 97% versus 58%, and for Ta lesions the respective detection rates were 97% versus 88%. The rate of false positives with HAL PDD was 13% and 10% for white light. The European trial confirmed the benefit of using HAL for the diagnosis of bladder tumour, particularly for CIS, whether solitary or associated with exophytic lesions.

Further confirmation of the efficacy of HAL PDD has come from a more recent multicentre study in the USA (PCB302/01) [24,25], in which 311 patients underwent white-light cystoscopy followed by HAL PDD (93 training patients were excluded from the analysis). Lesions were mapped, then resected for pathology; two reference pathologists reviewed all of the slides. Again, the Storz D-light system was used. Among 196 patients in the intent-to-treat group, Ta was found in 108 (55.1%); in six patients, the lesion was detected only by HAL PDD. Multiple tumours were detected in 54 patients; in 31 of the 54, at least one more Ta tumour was detected by HAL PDD than by white-light cystoscopy. T1 tumours were found in 22 patients, with no statistical difference in detection rates between HAL PDD and white-light cystoscopy. Overall, 218 Ta tumours were detected, 207 by HAL and 181 by white light (95% vs 83%). CIS was detected in 58 of 196 patients (29.6%); solitary CIS in 18, and associated with an exophytic tumour in 35. Of the total of 113 CIS lesions, 104 were detected by HAL PDD (92%) and 77 by white-light cystoscopy (68%).

According to the findings of the three studies outlined above, HAL cystoscopy is easy to perform,
improves the detection rate of bladder tumours, including CIS, and is an important tool in the management of bladder cancer.

Because of the high rate of tumour recurrence, follow-up endoscopy is an important aspect of the management of patients with bladder cancer. Two studies have compared the efficacy of rigid versus flexible endoscopy, using HAL versus white light [26,27]. Witjes et al used the Storz D-light system for cystoscopy just before TURB in 20 patients, 19 of whom had a total of 27 histologically confirmed lesions and 1 patient with no proven lesions [26]. Nineteen of the 27 lesions were detected by flexible HAL, 23 by rigid HAL, and 20 by rigid white light. A study by Loidl et al included 45 patients who underwent white-light and HAL flexible and rigid cystoscopy, using the Combilight [27]. Of 41 patients who had exophytic tumors, 39 were detected by HAL flexible cystoscopy, and 40 were detected by HAL rigid cystoscopy; CIS, which was confirmed in 17 patients, was detected in 14 patients by HAL flexible cystoscopy, in 15 by HAL rigid cystoscopy, in 11 by white-light flexible cystoscopy, and in 13 by white-light rigid cystoscopy.

These two studies suggest that HAL flexible cystoscopy is more effective than white-light flexible cystoscopy in the detection of bladder tumours; but may be equivalent to rigid white-light cystoscopy and less efficient than HAL rigid cystoscopy. Further studies are required, and there may be a need for improvement to endoscope technology, particularly in the case of flexible designs.

3.4. Technical aspects and current experience of photodynamic diagnosis and ongoing development

3.4.1. Technical aspects of the procedure
PDD is typically performed 1 h after instillation of HAL. Different light-source systems that are able to adapt to rigid or flexible endoscopes are now available. Although PAPs fluorescence is activated by a specific excitation band in a range of 390 nm to 470 nm, manufacturers propose specific combinations of light guide, cystoscopes, and camera, which cannot be mixed with standard components [28]. Special care has to be taken not to damage the light guide or the endoscope, which could result in a reduction of the instrumental light output. Therefore, correct maintenance of the whole instrumentation is essential to the quality of the information obtained with PDD.

During the intervention, the bladder wall is smoothly unfolded under clear irrigation from the cystoscope, and the user-friendly light source allows close inspection of the bladder wall with either white light (standard cystoscopy) or blue light (fluorescence cystoscopy).

Tumour fluorescence is generally well demarcated and sparkling, except for some CIS lesions, which may appear as a reddish halo. By contrast, false fluorescence from nonmalignant, sometimes inflammatory tissue is not so well defined, appearing as pinkish patchy areas with blurred margins that run along blood vessels [28,29]. This appearance is mainly associated with tangential areas of illumination [29].

Either in previous ALA or specifically designed HAL studies, side effects following bladder instillation or bladder-wall illumination—for example, dysuria, haematuria, bladder pain, and bladder spasm—have been rarely reported, are nonspecific, and are probably not drug related [28]. The recent report of an anaphylactic shock 5 h after HAL instillation in one patient necessitates further appraisal for specific drug involvement [30].

3.4.2. Current experience of photodynamic diagnosis and ongoing development
Standard techniques probably underestimate the frequency of concomittant CIS, which in the recent EORTC analysis of 2596 patients with Ta and T1 bladder cancer was recorded in 9.4% of patients with T1G3 disease. Concomittant CIS is recognised as a poor prognostic factor with a 1-yr and 5-yr risk of progression probability of 29% and 74%, respectively [31]. PDD enhances the diagnosis of dysplasia and CIS in all presentations of the disease, with a detection rate of 91.1–97% [23,32]. The improvement in detection may affect treatment management in a significant proportion of cases [33].

The impact of PDD on the natural history of the disease is, however, more difficult to assess. Three of four ALA studies demonstrated a 2–4-fold reduction of the residual tumour rate with TURB-PDD by comparison with standard TURB [28], which is an important point for the risk of first recurrence and possibly for progression in T1 patients [34].

Although two long-term studies at 5 yr and 8 yr showed a positive impact of PDD on recurrence-free survival, this point is still debatable and should be assessed by further large-scale trials [28].

The weakness of PDD remains its specificity, which varies from 35% to 66% [28]. Observed differences are linked to technical factors (operator skill, tangential illumination of the bladder wall), time and modalities of previous treatments (scar, inflammation) or often remain not clearly defined (normal mucosa, hyperplasia) [28,35]. False positives may raise a problem of definition when urothelial premalignant changes, such as dysplasia are con-
sidered to be either false [35] or true positives [32]. On one hand, the presence of false positives mainly at the trigone or the bladder neck may alter PDD exploration, but on the other hand, there is no clear indication to rule out a biopsy in the presence of a positive fluorescence [35]. In addition, the impact of cellular cycle alterations on the heme biosynthetic pathway observed sometimes on normal mucosa remains unknown [28] and suggests the existence of “false” false positives. Ongoing research aims at improving specificity by the use of different methods, such as optical coherence tomography or tissue image magnification [36].

Correct maintenance of the instrumentation is essential to the quality of information obtained with PDD. Despite some variability in specificity, the sensitivity of the method in detection of CIS remains as high as 90%. Therefore, PDD may be used as a precise tool for guidance of biopsy and transurethral resection of the bladder. Ongoing research into HAL-based PDD aims to improve specificity through the development of techniques combining tissue image magnification and spectral analysis.

4. Conclusions

Due to a constant and high sensitivity, PDD with HAL (the only photosensitiser licensed in Europe for this indication) enhances the detection of bladder tumours and mainly flat urothelial malignancies by comparison with conventional white-light cystoscopy alone. Ongoing research aims at improving the method specificity by different tissue characterisation techniques. However, the impact of HAL-PDD on non-muscle-invasive bladder cancer risk of progression needs to be further consolidated.

Conflicts of interest

The authors have nothing to disclose.

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