Photodynamic Diagnosis in Urology: State-of-the-Art

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Abstract

Objectives: To provide an overview on the methodology and clinical relevance of fluorescence diagnosis with exogenous fluorochromes or fluorochrome prodrugs in urology.

Methods: The methodology is summarised on the basis of our experience and the relevant literature. Clinical results and perspectives are reported and concluded after we scanned and evaluated sources from PubMed. Search items were “aminolev*” or “hypericin” or “photodyn*” or “porphyrin” or “fluorescence” or “autofluorescence” and “bladder” or “prostate” or “kidney” or “peni*” or “condylo*”. Some literature was also obtained from journals not indexed.

Results: A large number of clinical trials have shown that photodynamic diagnosis (PDD) improves the ability to detect inconspicuous urothelial carcinoma of the bladder. Fluorescence diagnosis has recently been approved in Europe for the detection of bladder cancer after instillation of a hexaminolevulinate (Hexvix®) solution. PDD is recommended by the European Association of Urology for the diagnosis of carcinoma in situ of the bladder. To date, the major weakness of PDD for the detection of bladder cancer is its relatively low specificity. Initial results with PDD for the detection of penile carcinoma, prostate cancer, kidney tumours, and urethral condylomata are promising.

Conclusions: To determine the actual impact of PDD on recurrence and progression rates of bladder cancer, further long-term observational studies are necessary. These studies also will clarify whether PDD is cost efficient.

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1. Introduction

Photodynamic diagnosis (PDD) involves fluorescence to localise abnormal tissue. Therefore, this procedure is also referred to as fluorescence diagnosis or fluorescence photodetection. Representing an additional optical recognition criterion, PDD reveals neoplastic lesions that cannot be seen by means of conventional methods. The value added depends on the selective accumulation of fluorochrome and on how well interfering optical tissue inhomogeneities can be considered or eliminated.

In urology, clinical interest in PDD mainly has focussed on the improved detection of hardly visible urothelial bladder cancer. Small papillary tumours and flat urothelial lesions can easily be overlooked during conventional white light cystoscopy [1]. Preventing correct and early treatment, missed diagnosis of high-grade flat lesions such as carcinomas in situ (CIS) has a decisive impact on case outcome. In addition, incomplete resection results in “recurrences,” that is, merely previously undetected tumours.

Within recent years, PDD of bladder cancer has found its way into widespread clinical use. The first exogenous fluorochrome, hexaminolevulinate, has obtained approval for the detection of bladder cancer in 26 European countries. According to the 2006 European Association of Urology (EAU) guidelines, PDD has been accepted as a method to reveal areas in the bladder that are suspicious of CIS or of developing papillary tumour that cannot be seen with white light cystoscopy. Nevertheless, “this investigational method has not yet been implemented on a regular basis in daily practice” (EAU guidelines on TaT1 [non–muscular-invasive] bladder cancer, 2006).

To examine the current status of PDD in urology, this review summarises development, methodology, and clinical experience with special emphasis on fluorescence diagnosis of bladder cancer.

2. Physics behind PDD

Fluorescence is caused by the interaction of light (photons) with the outer electrons of molecules. Molecules that are electronically excited by absorption of a photon of appropriate wavelength have several possibilities to return to their ground state. One option is to emit a secondary photon. Molecules making use of this relaxation path efficiently are called fluorochromes. Fluorochromes absorb light with a high energy per photon and re-emit light with a lower energy per photon, producing a shift in colour between excitation and fluorescence light.

Optical filters can block backscattered excitation light and transmit selectively within the wavelength bands of fluorescence emission. This is a well-known procedure used in fluorescence microscopy. Fluorescent markers, bound to antibodies or intracellularly synthesised, can be detected with high sensitivity because the unspecific background light is weak. Thus, these are the advantageous features of fluorescence detection: lack of background signal and specific targeting.

Specific targeting for medical diagnostic purposes implies a contrast in fluorescence of diseased versus normal tissue. This might be achieved with endogenous tissue fluorochromes (autofluorescence) or by delivering substances that cause specific fluorescence staining.

3. Autofluorescence

Among the most efficient endogenous fluorochromes are collagen, elastin, nicotinamide adenine dinucleotide, flavin adenine dinucleotide, lipofuscin, tryptophan, and keratin. Some of these fluorochromes are located in the subepithelial connective tissue layer of the corresponding tissue. The intensity of the perceptible autofluorescence is thus partly determined by the thickness of the epithelial cell layer covering connective tissue. Increased proliferative activity of malignant cells thereby results in reduced autofluorescence. Attempts to exclusively exploit endogenous fluorescence for tumour recognition have been made [2,3] and have gained some clinical acceptance with regards to the detection of early-stage bronchial cancer.

Early clinical studies have shown that autofluorescence may be a promising additional tool to discriminate neoplastic from benign lesions of the bladder and penis [2,4]. To date, this diagnostic method has not found its way into the routine practice of urologists.

4. Exogenous drugs for fluorescence

The application of exogenous drugs for fluorescence diagnosis relies on a positive fluorescence staining of malignant or premalignant tissue. Most of the substances that already were applied in the clinic environment are photosensitisers. Apart from showing fluorescence, photosensitisers also exert a phototoxic action, which is used for photodynamic
therapy (PDT). A recent review, dealing with PDT in urology, is given by Pinthus et al [5]. PDT will not be explicitly included in this article, but readers may keep in mind this additional potential of the fluorochromes discussed. Clinical experience in the use of fluorescence diagnosis in urology has been reported for tetracycline, hypericin, and the porphyrin-related substances hematoporphyrin derivative, Photofrin®, 5-aminolevulinic acid (5-ALA) and, most recently and successfully, its hexyl ester hexaminolevulinate (Hexvix®). For tetracycline fluorescence excitation, UV excitation is necessary and corresponding instruments were developed in the early 1960s [6], but UV cystoscopy was abandoned in the 1970s. Hypericin and porphyrins can efficiently be excited by visible violet light (ca. 400 nm) and emit red fluorescence (590–700 nm).

Detection of fluorescence signals from tissue is, unfortunately, not as straightforward as in fluorescence microscopy. Excitation light incident on a tissue surface penetrates several tissue layers where it is multiply scattered and absorbed from inhomogeneously distributed absorbers, mainly haemoglobin. The same is true for fluorescence light excited somewhere inside the tissue. It is, therefore, not astonishing that the detectable fluorescence intensity from an endogenous or exogenous fluorochrome is not a reliable quantitative measure of its local concentration. Additionally, in most clinical situations, the investigated tissue is excited inhomogeneously and from an arbitrary distance and angle. By applying different wavelengths for excitation or detection and establishing appropriate algorithms, several groups have tried to generate more reliable fluorescence signals for diagnostic fluorescence imaging [7,8].

The currently used clinical instrumentation, available from several manufacturers of endoscopes and light sources, is especially designed for fluorescence cystoscopy and displays red porphyrin fluorescence together with blue remitted light. The blue light serves as a reference. It corrects inhomogeneous illumination and distance variations. It also largely compensates for varying blood absorption and observation angles [9]. The wavelength of the blue reference light is chosen in a way to experience intermediate absorption in tissue compared to the high absorption at the excitation wavelength and low absorption at the emission wavelength. The identification of suspicious tissue by fluorescence occurs quite intuitively by the colour contrast of red fluorescence versus blue reference light. Normal tissue thus appears blue with a more or less greenish hue, originating from autofluorescence, whereas suspicious tissue is identified by its red colour (Fig. 1).

4.1. ALA and derivatives

Among the substances available for porphyrin-based fluorescence imaging, 5-ALA is the most widely used. It is a small molecule containing five carbon atoms, a zwitterion with an amino group on the one and a carboxylic acid group on the other end.

![Fig. 1 – Fluorescence (a) and white light (b) endoscopic image of a flat pTaG1 lesion adjacent to a small papillary tumour that was classified pTaG1 as well. Fluorescence staining was performed by instillation of 50 ml of a solution containing 1.5 g 5-aminolevulinic acid. Reproduced by permission of the Royal Society of Chemistry (RSC) on behalf of the European Society for Photobiology [13].](image-url)
It plays a natural role in the intracellular biochemical pathways as a heme precursor.

The administration of exogenous 5-ALA bypasses the rate-limiting step in the biosynthesis of heme, the synthesis of endogenous 5-ALA in the mitochondria. It thereby forces each enzyme in the pathway to produce its product with maximum available capacity. The critical bottleneck is the step from protoporphyrin IX (PpIX) to heme, the insertion of a ferrous ion into the porphyrin ring, catalysed by the enzyme ferrochelatase. Thus, exogenously applied 5-ALA can induce significant intracellular levels of PpIX. PpIX is an effective photosensitiser and the only fluorescent substance in the pathway.

The transient accumulation of excess PpIX preferentially occurs in neoplastic or highly proliferating cells [10]. Among the causes of this phenomenon, reduced activity of ferrochelatase and a relative enhancement of porphobilinogen deaminase activity are considered to be the decisive factors [11,12]. Thus, it is possible to use 5-ALA–induced fluorescence to locate malignant and premalignant lesions.

5-ALA can be administered topically in cream or gel formulations, as an aerosol for inhalation, or as an instillation liquid as well as systemically, preferentially by oral delivery. A comprehensive overview of the basic principles and clinical applications of 5-ALA is given in the book by Pottier et al [13]

One of the drawbacks of 5-ALA–based PDD is the relatively fast photobleaching of PpIX. During irradiation with fluorescence excitation light, the photosensitiser PpIX can itself be a victim of the aggressive oxygen generated. It is then destroyed and lost for further “photodynamic purpose” (fluorescence or phototoxicity). To prevent practical limitations, instrumentation must be highly sensitive for fluorescence detection and unnecessary light exposure must be avoided.

Another drawback of 5-ALA is its low lipophilicity, preventing thorough tissue penetration. With the aim of enhancing lipophilicity, ester derivatives have been synthesised. For use in dermatology, the methyl derivative gained approval (Metvix®, Photocure ASA, Oslo, Norway), whereas for bladder cancer detection the hexylester hexaminolevulinate (Hexvix, GE Healthcare, London, United Kingdom) proved to be superior. Following intravesical application, hexaminolevulinate has shown deeper penetration into the urothelium and production of a higher PpIX concentration at significantly lower prodrug concentrations compared to 5-ALA [14]. The ester derivatives of 5-ALA cross the cell membrane rather by passive diffusion in contrast to the parent compound, which is transported intracellularly by active uptake via β-amino acid, γ-aminobutyric acid or PEPT1 and PEPT2 membrane transport proteins [15]. Passive diffusion, in this case, leads to a considerably faster and more efficient uptake. Nonspecific esterases in the cells are believed to at least partly release the parent compound to enter the heme biosynthesis pathway. It can, however, not be excluded that the enzymes also may act on the esters directly, finally producing esterified PpIX. For this reason, the fluorochromes synthesised on delivery of hexaminolevulinate are usually referred to more generally as “photoactive porphyrins” (PAPs). Unlike 5-ALA, hexaminolevulinate is not suitable for systemic application.

4.2. Hypericin

Hypericin, a hydroxylated phenanthroperylenequinone, is one of the ingredients that causes the phototoxic effects of the Hypericum perforatum L plant (St John’s wort) [16]. Hypericin fluorescence can be excited and detected with the same equipment as used for porphyrin fluorescence. A considerable practical advantage of hypericin over porphyrins is its significantly reduced photobleaching, allowing for longer investigation times. Pure hypericin, which is synthetically produced nowadays, is characterised by a number of drawbacks, such as low solubility, costly production, and to some extent lack of stability in solution [16]. In vitro studies have shown that methanolic extracts from the H. perforatum plant may offer less expensive alternatives [17]. Solubility could successfully be increased by nontoxic additives, such as pyrrolidones [18].

5. History of applying fluorescence diagnosis in urology

First attempts with tetracycline fluorescence were performed in 1957 [19]. In 1975, the haematoporphyrin derivative (HpD) was initially proposed for bladder cancer detection by Kelly [20]. Photofrin®, a drug derived from HpD, was first applied for bladder cancer imaging by Baumgartner et al in 1987 [7], after Jocham et al, Nseyo et al, and Dougherty had published early works on PDT of bladder cancer with Photofrin in 1985 [21–23].

The main drawback associated with these synthetic porphyrins, at least for exclusively diagnostic application, is a prolonged skin photosensitisation. Low-dose drug regimes, which overcome this side-effect [24,25], necessitate complicated instrumentation [25].
Following publication of first reports on the clinical suitability of the 5-ALA porphyrin prodrug by Kennedy et al in 1990 [26], topical application of 5-ALA as an intravesically administered solution was first implemented clinically by Kriegmair et al in 1992 [27]. Because the fluorescence intensity obtained was much brighter than with low-dose Photofrin, instrumentation could be simplified.

6. Fluorescence diagnosis of bladder cancer

6.1. Equipment

Some manufacturers of endoscopes and light sources offer equipment for fluorescence cystoscopy, comprising

- Light source: high-power endoscopic light source with integrated excitation filter, providing excitation light in the range of 380–470 nm. The light source can be switched between white light and fluorescence modes and communicates with the camera controller.
- Light guide: special light guide for efficient excitation light coupling to cystoscope.
- Cystoscope: including optimised fibre bundles for illumination and observation filter in the eyepiece (alternatively, filter is inserted in the camera optics). Rigid and flexible versions are available. Video endoscopes suitable for fluorescence imaging are in development.
- Camera: high-sensitivity version of the endoscopic camera, including a special “fluorescence mode” with preset gain values and corresponding communication with the light source.

Although the equipment looks similar to standard cystoscopy equipment, each of the components is specialised and care must be taken to not mix fluorescence equipment with standard components.

In fluorescence mode, brightness is a limiting factor because fluorescence efficiency of the fluorochromes amounts to only a few percent. Thus, the quality of the video images is somewhat reduced compared to white light video, or motion artefacts have to be considered due to frame integration. Additionally, old lamps and light guides should readily be replaced. The surgeon should also provide for clear irrigation liquid and maintain sufficiently close distance to the bladder wall.

Urine shows bright green fluorescence, which results in blurring when in fluorescence mode, if the bladder was not accurately voided prior to cystoscopy.

Porphyrin fluorescence is quite efficiently bleached during light exposure, especially with excitation light, thereby contributing to limiting the observation time. Hypericin fluorescence is stable under practical conditions of fluorescence cystoscopy.

6.2. Clinical studies

A large number of clinical trials have shown that PDD improves detection of bladder cancer (Table 1). In the published studies, the sensitivity of fluorescence cystoscopy is consistently superior to white light cystoscopy. The mean value of the sensitivities

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>No. of patients</th>
<th>Agent</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kriegmair, 1996 [73]</td>
<td>104</td>
<td>ALA</td>
<td>96.9</td>
<td>66.6</td>
</tr>
<tr>
<td>Koenig, 1999 [52]</td>
<td>55</td>
<td>ALA</td>
<td>87</td>
<td>59</td>
</tr>
<tr>
<td>Riedl, 1999 [74]</td>
<td>52</td>
<td>ALA</td>
<td>94.6</td>
<td>43</td>
</tr>
<tr>
<td>Filbeck, 1999 [75]</td>
<td>120</td>
<td>ALA</td>
<td>96</td>
<td>35</td>
</tr>
<tr>
<td>Zaak, 2002 [76]</td>
<td>713</td>
<td>ALA</td>
<td>97</td>
<td>65</td>
</tr>
<tr>
<td>Grimbergen, 2003 [42]</td>
<td>160</td>
<td>ALA</td>
<td>97</td>
<td>49</td>
</tr>
<tr>
<td>Hungerhuber, 2007 [77]</td>
<td>875</td>
<td>ALA</td>
<td>92</td>
<td>41.4</td>
</tr>
<tr>
<td>Jichlinski, 2003 [78]</td>
<td>52</td>
<td>HAL</td>
<td>96</td>
<td>43</td>
</tr>
<tr>
<td>D’Hallewin, 2002 [79]</td>
<td>87</td>
<td>Hypericin</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Sim, 2005 [50]</td>
<td>41</td>
<td>Hypericin</td>
<td>82</td>
<td>91</td>
</tr>
</tbody>
</table>

The em dash indicates missing data.
PDD = photodynamic diagnosis; WLC = white light cystoscopy; ALA = 5-aminolevulinic acid; HAL = hexaminolevulinate; CIS = carcinoma in situ.
for fluorescence cystoscopy is 93% (range: 82–97%), compared to 73% (range: 62–84%) for white light cystoscopy. Tritschler et al showed the sensitivity of PDD to be higher than the sensitivity of the urine marker NMP221BladderChek1 test, voided cytology, and washing cytology, respectively [28].

Until now, five prospective multicentre studies comparing fluorescence-guided transurethral resection (TUR) and conventional TUR using white light cystoscopy have been published [29–33]. Three of these trials [29,31,32] were randomised, whereas the remaining two studies [30,33] focussed on inter-patient comparison. All five studies showed that PDD is more effective than white light cystoscopy for detecting malignant bladder lesions, in particular CIS. As a consequence of the improved detection rate, 17% of patients in the study managed by Jocham received more appropriate treatment following fluorescence-guided cystoscopy [32].

The completeness of resection using PDD has been studied and three of the four controlled, phase 3 studies proved that the number of tumours detected at second-look TUR is significantly reduced in patients following fluorescence-guided cystoscopy [29,34–36] (Table 2).

With regard to the recurrence rate, the presented studies have conflicting results. Three of five studies have shown that fluorescence-guided TUR enhances the recurrence-free survival rate after 24 mo (recurrence-free survival rate following PDD versus white light cystoscopy: 40–88% vs. 28–64%, respectively) [37–39]. Two studies recently presented at the congresses of the EAU and the American Urological Association [29,40], however, did not reveal any difference in recurrence rates. Possibly biasing the evaluation of PDD as a diagnostic tool, these trials have included topical recurrence prophylaxis. Publications interpreting the data are not yet available.

Until now, results of two large prospective, randomised trials on long-term benefit of 5-ALA–induced fluorescence diagnosis versus white light cystoscopy have been published [37,39] (Table 3). Follow-up in these studies was 5 and 8 yr, respectively. Both studies conclude that fluorescence-assisted TUR increases recurrence-free survival of patients suffering from non–muscle-invasive urothelial carcinomas of the bladder.

In the published clinical trials, the selection criterion for patient inclusion was suspected or suspected or known urothelial carcinoma of the bladder. As far as data are available, both patients with primary and recurrent bladder cancer were included in all studies. The reported proportion of patients with primary cancer varied between 32% [30] and 82% [37].

To date, the major weakness of PDD for the detection of bladder cancer is its relatively low specificity. The specificity of fluorescence-guided cystoscopy reported in comparative studies is not better or even lower than the specificity of standard white light cystoscopy (Table 1). In the study published by Tritschler et al, the specificity of PDD is even lower than the specificity of voided urine cytology [28]. False-positive fluorescence may be induced by inflammation [41] or recent intravesical

### Table 2 – PDD using 5-ALA versus WLC: residual tumour rate at second-look TUR

<table>
<thead>
<tr>
<th>Author, year of publication</th>
<th>No. of patients</th>
<th>Residual tumour rate, % PDD</th>
<th>Residual tumour rate, % WLC</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riedl, 2001 [36]</td>
<td>102</td>
<td>16</td>
<td>39</td>
<td>0.005</td>
</tr>
<tr>
<td>Kriegmair, 2002 [35]</td>
<td>129</td>
<td>32.7</td>
<td>53.1</td>
<td>0.031</td>
</tr>
<tr>
<td>Filbeck, 2002 [34]</td>
<td>191</td>
<td>4.5</td>
<td>25.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alken, 2007 [29]</td>
<td>604</td>
<td>29</td>
<td>29.2</td>
<td>—</td>
</tr>
</tbody>
</table>

The em dash indicates missing data.
PDD = following photodynamic diagnosis; WLC = following white light cystoscopy; TUR = transurethral resection.

### Table 3 – PDD using 5-ALA versus conventional WLC: long-term follow-up

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients available for efficacy analysis</th>
<th>Recurrence-free survival rate, % PDD</th>
<th>Recurrence-free survival rate, % WLC</th>
<th>Median follow-up, mo PDD</th>
<th>Median follow-up, mo WLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniltchenko [39]</td>
<td>102</td>
<td>41</td>
<td>25</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>Denzinger [37]</td>
<td>191</td>
<td>71</td>
<td>45</td>
<td>86</td>
<td>83</td>
</tr>
</tbody>
</table>

PDD = following photodynamic diagnosis; WLC = following white light cystoscopy.
therapy [42]. In addition, normal mucosa may contain a minimal amount of endogenous PpIX. Viewed with an acute angle, the thin normal mucosa represents a thick layer for the observer and may thus cause the impression of fluorescence. This preferentially occurs when investigating the bladder neck, trigone, or diverticula [43].

Whether fluorescence of histologically proven benign lesions is caused by early malignant genetic alterations is still the object of research. Molecular analyses indicate that at least some of the false-positive hyperplastic urothelial lesions may have to be considered tumour precursors missed by conventional cystoscopy [44]. Immunohistochemical staining for p53 and p16, however, did not show a difference between false-positive fluorescent lesions and benign lesions [43].

Two clinical studies compared the technical equipment. These studies indicate that PDD using rigid cystoscopes results in a higher tumour detection rate than using flexible cystoscopes (85–94% vs. 70–89%, [45,46]).

Prospective randomised trials that compare the efficacy of the different exogenously applied fluorochromes for PDD of urothelial carcinomas are still lacking. A study comparing hexaminolevulinate and 5-ALA for the detection of bladder cancer specified the derivative to be superior by showing higher tumour selectivity, lower efficient concentration, shorter administration time needed and deeper tissue penetration obtained [47]. Evidence indicates that specificity of hypericin is superior to specificity of 5-ALA and hexaminolevulinate [48–50].

6.3 Guidelines and recommendations

Due to the superior sensitivity of this diagnostic modality, PDD is recommended by the EAU as well as the Austrian Association of Urology. According to the EAU guidelines, fluorescence cystoscopy should be considered for the diagnosis of CIS of the bladder (grade B recommendation; EAU guidelines [51]). The consensus board of the Austrian Association of Urology recommends performing fluorescence-guided cystoscopy in patients with cytology results suspicious of urothelial carcinomas but normal findings in white light cystoscopy and in follow-up cystoscopy for high-risk urothelial carcinomas, especially for CIS.

6.4 Side-effects

All studies concurrently available showed that PDD of bladder cancer using exogenous drugs for fluorescence diagnosis is well tolerated [31–33,50,52]. Following intravesical instillation, 5-ALA, hexaminolevulinate, and hypericin are absorbed systemically in very low concentration only [53–55]. Therefore, the side-effects of PDD are mainly limited to local symptoms such as dysuria, haematuria, bladder pain, and bladder spasm [32]. With regard to these symptoms, there is no difference between patients undergoing fluorescence endoscopy and white light cystoscopy [35]. The recently reported case of anaphylactic shock 5 h after intravesical exposure to hexaminolevulinate, however, clearly necessitates further assessment [56].

6.5 Fluorescence cytology

Initial investigations have been made with fluorescence microscopy. In a standard setting (405–435 nm excitation, detection with long-pass filters at approximately 460 nm), porphyrin-containing cells show red fluorescence, whereas unstained cells are identified by their weak green autofluorescence. Red blood cells appear as small dark spots.

In an attempt to simplify the analysis of bladder washing specimens, a special instrument was designed to spectrally resolve porphyrin fluorescence [57]. Preliminary results with ex vivo fluorescence cytology using 5-ALA or hypericin and flow cytometry using hexaminolevulinate suggest that this diagnostic modality may be a useful adjunct to conventional urinary cytology in detecting malignant urothelial cells [57–59].

7. Fluorescence diagnosis of non-urothelial tumours

Because the principle of tumour-selective fluorescence upon delivery of 5-ALA is not restricted to bladder cancer, it was investigated for other urologic applications, too. Urethral condylomata acuminata detection was first reported by Schneede et al [60], after Fehr et al and Ross et al had shown selective staining of such lesions on the vulva and the shaft of the penis [61,62]. Fluorescence diagnosis of the urethra is performed 1 h after urethral instillation of 0.1% solution of 5-ALA. In a single-institution trial, fluorescence urethroscopy detected additional subclinical human papilloma virus (HPV) lesions in 13 of 43 men [60]. A study of neodymium:yttrium-aluminum-garnet (Nd:YAG) laser coagulation of urethral condylomata following conventional white light urethroscopy alone and white light endoscopy in addition to fluorescence urethroscopy after topical application of 5-ALA showed fewer recurrences in
the fluorescence-controlled group (21.3% vs. 47.3%) [63].

Early clinical experience indicates that fluorescence-guided Nd:YAG laser therapy using topically applied 5-ALA assists in better discriminating the tumour margin, thus resulting in more reliable destruction of all neoplastic tissue in penile-sparing surgery [4]. Because, following the oral administration of 5-ALA, PpIX is also accumulated in tumour-bearing lymph nodes of patients with penile carcinomas, PDD may also provide a useful adjunct to localise metastatic disease in lymphadenectomy [64].

Fluorescence diagnosis of renal cell carcinoma was first reported by Popken et al in 1999 [65]. In a clinical pilot study, 5-ALA had been applied systemically 4–6 h prior to organ-preserving tumour resection. In eight of nine renal tumours, resection borders could be clearly demarcated by PpIX fluorescence. Despite these promising results, no further clinical experience with PDD of kidney cancer has been reported to date. Because surrounding tissue precludes fluorescent photodetection, PDD of renal cell carcinoma is limited to peripheral tumours.

Applicability for diagnosis and treatment of prostate carcinomas is a matter of ongoing clinical studies. First cases were already reported by Zaak et al in 2003 [66]. Fluorescence microscopy of cryosections obtained from cancer-bearing prostates after radical surgery showed highly selective PpIX accumulation in cancer epithelium versus normal glandular epithelium and connective tissue.

8. Future perspectives

Instrumentation for fluorescence diagnosis will follow the general trend towards improved resolution (high-definition TV-standard cameras, video endoscopy). The development of semiconductor-based light sources for fluorescence excitation in combination with video endoscopy may provide a user-friendly equipment. Digital image processing on fluorescence images and overlay on intermittently acquired white light images may further improve diagnostic accuracy [67,68]. Especially for systems used in an outpatient environment, a “quality check feature” is important to avoid false diagnosis due to improperly working equipment. The major task will be to enhance the specificity of PDD.

9. Discussion and conclusions

PDD of bladder cancer has entered the era of prospective randomised trials. First results of long-term follow-up studies are available. Unanimously, all studies report that fluorescence cystoscopy significantly improves the endoscopic detection of bladder cancer as compared to standard white light cystoscopy. The enhanced diagnosis of the sometimes hardly visible CIS by PDD is one of the most remarkable benefits of this method and improves management of patients suffering from this disease. Multivariate analyses have shown that presence of CIS is an independent unfavourable prognostic factor, increasing the risk of progression. Particularly bacillus Calmette-Guérin failures need meticulous follow-up and individualised therapy [69]. Therefore, fluorescence cystoscopy should be considered particularly for the diagnosis of CIS of the bladder and in follow-up cystoscopy for high-risk urothelial carcinomas. The high sensitivity of PDD makes it feasible to refrain from taking random biopsies or TUR, if there is no suspicious fluorescence in PDD.

Patients with multifocal stage Ta bladder tumours also profit from PDD. Tumour “recurrence” may be due to the persistence of residual tumour in the bladder after an incomplete TUR or a lesion that has been overlooked during first endoscopy [70]. The more complete first resection under PDD control can make a second-look resection in patients with Ta bladder tumours unnecessary. Because 5-ALA and hexaminolevulinate do not penetrate much deeper than 1 mm, however, fluorescence cannot indicate invasion depth. Therefore, a second transurethral resection is indicated in T1 tumours to rule out muscle invasion.

The adequacy of the TUR also has an important impact on the percentage of patients with superficial bladder cancer having a recurrence at first follow-up cystoscopy after initial TUR [70]. It has been shown that the recurrence at any site in the bladder at the first follow-up cystoscopy after TUR is one of the most important prognostic factors for time to progression [70–72]. Therefore, PDD might be most advantageous for patients with primary tumours. Large and multicentre studies, however, comparing the outcome of patients with primary and recurrent cancer following PDD are still warranted.

To determine the actual impact of PDD on recurrence and progression rates, further long-term observational studies are necessary. These studies also will clarify whether PDD is cost efficient.

Promising initial results with PDD for the detection of penile carcinoma, prostate cancer, kidney tumours, and urethral condylomata justify further clinical studies.
Conflicts of interest

The authors have nothing to disclose.

References


Early cancer detection is an essential prerequisite of successful therapy. Despite an effort in many organ locations the principles of photodynamic diagnosis (PDD) have been applied mostly in bladder cancer. There is no doubt that fluorescence cystoscopy using 5-aminolevulinic acid or hexyl ester hexamethylenlevulinate improves the detection of bladder cancer as is thoroughly summarized by Jocham et al. Its efficacy was observed in different clinical situations and using both rigid and flexible endoscopes. There is, thus, no surprise that PDD is routinely used in an increasing number of centers. However, many aspects remain that must be considered to be able to exploit the method entirely:

1. Although some smaller prospective randomized trials showed its positive impact on recurrence...
rate in non–muscle-invasive tumors, no information is available about progression and survival rates. In fact, the major benefit of the method is expected in aggressive tumors where the aspects of progression and survival must be considered. The results of prospective randomized multicenter trials based on clearly defined end points and patient population are absolutely required.

2. The cost efficiency of PDD used in individual situations along with initial detection, transurethral resection, or follow-up cystoscopy must be determined. This will help us specify its indications and incorporate it precisely in currently used schedules of bladder cancer management.

3. The biologic background of the method is not completely understood. The explanation of principles of selective accumulation of protoporphyrin IX in tumor cells, of laser-induced autofluorescence, and of interactions between light and tissue are necessary to use the method totally and improve its specificity [2]. Together with development of new technologies we could expect more sophisticated detection tools that can overcome the user dependence of currently used techniques and even offer the possibility of real-time assessment of tissue pathology in vivo [3].

References


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Editorial Comment on: Photodynamic Diagnosis in Urology: State-of-the-Art
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The ultimate goal in the management of superficial bladder cancer is the prevention of disease recurrence and progression. Recent advances in photodynamic diagnosis (PDD) render this currently underused diagnostic technique an additional important tool in achieving this goal. Many of the recurrent superficial bladder cancers are probably undetected tumors that were not initially resected rather than recurrent new lesions. Consequently, it is reasonable to state that fluorescence-guided cystoscopy has significantly higher tumor detection rates than standard surveillance cystoscopy and that this can be translated to better patient care [1]. It seems, however, that the main obstacle in adopting PDD to routine urologic practice is the general lack of familiarity with it. The comprehensive review of Jocham et al clearly assists in easing this task [2]. It should be emphasized that, though efficient in reducing recurrence rates of superficial bladder cancer and allowing better detection of carcinoma in situ (CIS), the impact of PDD on the progression of these tumors remains to be determined. Another caveat of PPD of urothelial bladder carcinoma is its relatively low specificity. Although this may impede its use for diagnostic purposes in patients who undergo their first work-up for hematuria, it is not the case for patients with high-risk urothelial cancer (eg, patients with previous CIS or multifocal or large Ta bladder cancers). Although not published yet, PDD can be potentially very useful in the investigation of positive urine cytology in the absence of evident disease in white light cystoscopy and normal upper tracts.

In the current era of organ-sparing approaches in surgical uro-oncology, PDD can be an exciting potential adjunctive tool. Accordingly, the management of penile cancer can be complemented by PDD, specifically in defining the true margins of the lesion in penile-sparing surgery [3]. Similarly, preliminary promising results were demonstrated for partial nephrectomy of peripherally located kidney cancers [4]. Whether PDD can be used for the intraoperative detection of positive margins at the time of radical prostatectomy for prostate cancer or even in those selected cases of prostate-sparing radical cystectomy for bladder
cancer remains to be determined in specially designed clinical trials.

References


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