PHOTODYNAMIC DIAGNOSIS IN UROLOGY: STATE OF THE ART

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Summary.- High grade NMIBC remains a treatment challenge for urologists. WLC is widely regarded as the gold standard for detection and TUR. PDD may offer superiority to WLC in terms of detection, recurrence free survival and overall cost, but the current data must be scrutinized closely. Nearly all trials comparing PDD to WLC have shown an advantage in overall tumor detection with photodynamics and thus may lead to better treatment strategies in these patients.

Resumen.- El tumor vesical no infiltrante de la muscular (TVNMI) sigue siendo un desafío terapéutico para los urólogos. La cistoscopia con luz visible es ampliamente considerada el “gold estándar” para la detección y la RTU. El diagnóstico fotodinámico (PDD) puede ofrecer superioridad frente a cistoscopia con luz blanca en la detección, la supervivencia libre de recurrencia y el coste global, aunque los datos actuales deben ser analizados con cuidado. Casi todos los ensayos clínicos que comparan PDD y cistoscopia con luz blanca han mostrado una ventaja global en detección del tumor con la fotodinámica y así puede llevar a mejores estrategias terapéuticas en estos pacientes.

This review will focus on the results of a multitude of studies where PDD in combination with various photosensitizers was employed in the diagnosis and treatment of bladder cancer. The equipment, techniques and cost of these modalities will also be discussed.

Keywords: Photodynamic. Phototherapy. Urothelial carcinoma.

Palabras clave: Fotodinámica. Fototerapia. Carcinoma de células uroteliales.

INTRODUCTION

There were an estimated 70,980 cases of newly diagnosed bladder cancer in the United States and 14,330 bladder cancer deaths during 2009.
according to the National Cancer Institute. It is the fourth most common cancer among men and the ninth among women. Worldwide, there are approximately 350,000 new cases annually, making bladder cancer the sixth most common cancer in the world (1). The vast majority of the patients present as Ta and T1 tumors and less frequently as CIS. Collectively these are termed non-muscle invasive bladder cancer (NMIBC); however, this classification groups potentially life-threatening cancers with indolent acting tumors (2, 3). NMIBC is one of the most expensive diseases to treat because in many cases requires continued surveillance and multiple treatments.

The diagnosis of NMIBC has remained relatively constant since the 1930s, with white light cystoscopy (WLC) still the standard modality for surveillance of bladder cancer. Ideally, NMIBC can be managed endoscopically if a complete resection can be performed and if all tumors can be identified with high sensitivity. Current estimates place the number of bladder tumors missed by WLC at 10-20%, with the recurrence rates of NMIBC directly related to the performance of a complete transurethral resection (TUR). The use of urine cytology has attempted to make the diagnosis of NMIBC more sensitive, but it is not immediately available during endoscopy. Thus, it would be advantageous to find a method to supplement WLC that is both sensitive and specific and available at the time of endoscopy. As such, new techniques continue to emerge for the identification and treatment of NMIBC. Examples include narrow-band imaging, photodynamic diagnosis, and optical coherence tomography.

Photodynamic diagnosis (PDD) was first introduced in the 1960s and subsequently photosensitive drugs where introduced in the 1990s in an attempt to specifically identify tumor cells. Until recently, PDD has not been widely used due to the heterogeneity of results and lack of consensus guidelines. Many current studies show PDD to be a promising technology with reported increased detection rates and decreased tumor recurrence rates compared to conventional diagnostic modalities. This review will focus on the results of a multitude of studies where PDD in combination with various photosensitizers was employed in the diagnosis and treatment of bladder cancer. The equipment, techniques and cost of these modalities will also be discussed.

Current Management of NMIBC with WLC

NMIBC represents the majority of bladder cancers, with 70% of bladder tumors being confined to the urothelium (Ta) or lamina propria (T1) (2, 3). Of these, 15-61% will have recurrence and approximately 20% will eventually progress with muscle-invasive bladder cancer (4, 5). The most important prognostic factors for recurrence and progression are grade, stage and the presence of CIS (6, 7). A complete TUR supplemented with intravesical therapy represents the best chance for a cure of NMIBC. Several studies have demonstrated that an initial TUR with white light cystoscopy (WLC) can miss CIS or small papillary lesions (8, 9). Conversely, other studies have reported that WLC is very sensitive and specific for detecting the presence of malignancy, but is unreliable in determining tumor grade or stage (10). While the clinical significance of small papillary lesions has been questioned, the role of CIS in recurrence and progression has been established (6, 11, 12). Further, it has been shown that a re-staging TUR (re-TUR) is necessary when high grade T1 lesions are detected. Divrik et al reported that patients who underwent a re-TUR had a significantly longer recurrence-free-survival (RFS) than those who did not (13). Current EUA and AUA guidelines support re-TUR for a diagnosis of high grade or T1 bladder cancer (14, 15). The necessity of performing a complete TUR and obtaining a proper specimen when treating NMIBC cannot be overstated. Several centers have looked teaching proper TUR technique and demonstrated its importance (16, 17). Herr et al showed the need for a complete TUR in a recent series that included high grade Ta and T1 bladder cancer. On re-TUR, residual cancer was present in 65% of the high grade Ta tumors while higher stage tumors (T1 or T2) were found in 15% of cases. For T1 tumors, 88% had residual tumor at re-TUR and 30% were upstaged to muscle invasive disease (18). Other studies have shown residual tumor rates ranging from 28%-75% after initial resection and upstaging rates ranging from 7-30% (18-21). As the previously discussed studies have indicated, the ability to identify and completely resect all tumor is not currently optimal, and a technology that allows for improvements in these areas will benefit patient care.

PDD and Photosensitizers

Fluorescence endoscopy, referred to as photodynamic diagnosis (PDD), has been developed to enhance tumor detection by labeling neoplastic cells with drugs that form photoactive compounds. The concept relies on the differential uptake of drugs by neoplastic cells and their subsequent reaction to specific light wavelengths to produce detectable fluorescence (22). In 1975, Kelly et al was the first to show the preferential accumulation of a hematoporphyrin derivative (HPD) in bladder
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cancer cells (23). Years later, Kennedy introduced the prodrug, 5-aminolevulinic acid (5-ALA), which had the advantage of limiting systemic photosensitization (24). This prodrug is converted intracellularly to the active photosensitizer, protoporphyrin IX, which accumulates preferentially in malignant tissue. These molecules are excited by blue-violet light (400-600 nm range) and emit visible red light fluorescence (25). Koenig et al showed an accumulation of ALA in malignant tissue at a ratio of 20:1 compared to normal tissue (26). Since the advent of 5-ALA, several different derivatives have been developed to make a more lipophilic molecule with increased bioavailability and a longer half-life (27,28). The two main derivatives of ALA available commercially are methylaminolevulinate (MAL) (Metvix, Photocure ASLA, Oslo, Norway) and hexylaminolevulinate (HAL) (Hexvix, Photocure, Oslo, Norway)- (Hexvix, GE Healthcare, London, United Kingdom) (29-32). MAL has been used for dermatologic applications, while HAL has been studied in bladder cancer. HAL has recently been approved in Europe and the United States for the diagnosis of bladder cancer. A recently discovered photosensitizer, Hypericin, is a hydroxylated hentantroperylenquinone derivative from the plant St. John’s worth (Hypericum perforatum) and is being evaluated for endoscopic applications (33,34). Hypericin is administered intravesically and has shown longer fluorescence times, but with lower solubility. Hyperacin has shown high sensitivities and specificities for detecting CIS (94% and 95% respectively), which compares well to those obtained for 5-ALA and HAL photosensitizers (35). In order to make the molecule more water soluble, hypericin bound to polyvinylpyrrolidone (PVP-hypericin) was developed (36). Kubin et al reported an overall detection rate of 95% using this compound for recurrent or primary bladder cancer. In a small sample of patients with CIS, a sensitivity of 100% was shown using PVP-hypericin compared to only 33% in the WLC (37). Currently, 5-ALA or HAL remain the most studied compounds in PDD. Because of the relative lack of data exploring other compounds, this review will mainly focus on PDD in combination with these photosensitizers.

### Photodynamic Diagnosis Detection Rates

Multiple clinical trials have compared PDD to WLC. Most trials report a percentage increase in detection of PDD compared to WLC while other studies are designed with multiple arms and report their data as sensitivity or specificity. PDD performed with 5-ALA has demonstrated more effective detection of malignant lesions than conventional WLC. Almost 15 years ago, Kreigmair, described the potential of

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Tumor detection PDD</th>
<th>Tumor detection WLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grossman</td>
<td>108</td>
<td>95%</td>
<td>83%</td>
</tr>
<tr>
<td>pTa</td>
<td></td>
<td>95%</td>
<td>86%</td>
</tr>
<tr>
<td>pT1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jocham</td>
<td>146</td>
<td>96%</td>
<td>77%</td>
</tr>
<tr>
<td>All Tumor</td>
<td></td>
<td>95%</td>
<td>65%</td>
</tr>
<tr>
<td>CIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenzl</td>
<td>402</td>
<td>91%</td>
<td>90%</td>
</tr>
<tr>
<td>pTa</td>
<td></td>
<td>91%</td>
<td>59%</td>
</tr>
<tr>
<td>CIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fradet</td>
<td>58</td>
<td>92%</td>
<td>68%</td>
</tr>
<tr>
<td>CIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jchlinski</td>
<td>52</td>
<td>76%</td>
<td>46%</td>
</tr>
<tr>
<td>AllTumor</td>
<td></td>
<td>49%</td>
<td>5%</td>
</tr>
<tr>
<td>CIS</td>
<td>58</td>
<td>95%</td>
<td>76%</td>
</tr>
<tr>
<td>Reidl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*TABLE I. DETECTION RATES: STUDIES COMPARING PDD TO WLC.*
PDD using ALA, and reported a sensitivity of 100% and specificity of 68% for detecting bladder tumors in 68 patients (38). More recently, Hungerhuber demonstrated that 23.7% of malignant tumors were overlooked by WLC in his series but were detectable by PDD (26). A randomized, multicenter study by Alken et al and a large series by Zaak et al reported similar results (Table I) (39,40).

Many of the early studies with ALA showed increased bladder cancer detection compared to WLC, but had several problems. A high concentration of photosensitizer had to be instilled into the bladder for several hours prior to TUR due to low lipid solubility and short fluorescence time, and did not achieve a homogeneous distribution in superficial tumors (41). This led to the development of a more lipid soluble derivative, HAL. This has been shown to be effective with more intense fluorescence, increased stability, and decreased instillation times (30,42). Although HAL has been thoroughly investigated, the clinical results do not show a definitive advantage compared to ALA. Burger et al compared PDD using HAL and ALA, and did not show any superiority in residual tumor or RFS with a 2 year follow-up (43). However, he did report a statistically significant benefit with either of the two photosensitizers compared to WLC.

HAL has been utilized in the majority of recent studies. In three prospective multicenter trials using PDD, an increased overall detection rate of NMIBC ranging from 12-23% has been shown (Table I) (44-46). Jichlinski reported an increased sensitivity of PDD when compared to WLC specifically in the detection of CIS (45). Grossman showed and advantage to PDD in the detection rates of in Ta and T1 lesions using HAL compared to WLC, but not to the same extent as when detecting CIS (Table I) (44). Two additional studies focused on the detection rate of CIS using PDD. One phase III non-randomized prospective multicenter trial by Fradet reported CIS detection in 22 of 58 patients, whereas WLC detected CIS in only 8 of these patients (47). Liu et al showed an 11% advantage in the detection rate of CIS with PDD over WLC (48). Another multicenter study of 211 patients demonstrated a 97% detection rate with PDD using HAL versus 58% with WLC (49). In this series, 18 patients had CIS and no concomitant papillary tumors and of these, 6 were detected by HAL alone. Furthermore, of these 18 patients, 11 had tumor detection with negative cytology. Ray et al demonstrated a lack of specificity with cytology in a study of 23 patients (50). In this study, 74% of patients were previously treated for urothelial carcinoma and all had negative diagnostic evaluation (WLC, upper tract evaluation) but positive cytology. With the use of PDD, 6 patients showed bladder pathology, 5 with neoplasms and of those, 4 had CIS alone or concomitant NMIBC. Positive cytology with a negative standard hematuria evaluation is not uncommon and represents an additional setting where PDD may be specifically useful.

**Recurrence and Residual Tumor**

A complete TUR is essential for providing the optimal management of bladder cancer (51,52). In addition, the role of re-TUR has been established as standard practice for high-grade T1 bladder cancer because of the high residual tumor rates and high upstaging rates (18,20,21). In several studies, PDD assisted TUR has shown improvements in the residual tumor rate encountered at re-TUR as well as an increase in recurrence free survival (RFS) when compared to WLC. Dezinger et al randomized 301 patients who were to have a TUR to either WLC or PDD with 5-ALA. A repeat TUR was performed six weeks later. The residual tumor rate was significantly higher in the WLC arm (25.2%) versus the PDD group (4.5%). In the same study, the RFS was improved for the PDD group and was maintained over an 8 year follow-up (Table II) (53). This trial has the longest follow-up to date. An earlier randomized trial that produced similar results was published by Daniilichenko using a smaller series of patients (102) and a follow up of 5 years. In the WLC arm, 41% of the patients had tumor at re-resection, versus 16% in the PDD with ALA group. Again, a lower recurrence rate was maintained through the follow-up period. The study concluded that the decreased tumor recurrence was maintained due to improved visualization and a more complete initial TUR (54). Two additional studies using ALA also have reported similar results (55,56). A recently presented prospective, randomized, multi-institutional study by Stenzl et al consisting of 402 patients, compared WLC to PDD with HAL. This study showed improved detection of T1 and Ta lesions and a 36% rate of tumor recurrence at 9 months in PDD arm versus a 46% rate of recurrence in the WLC arm (57). Two randomized, multi-centre trials (Table II) did not show a difference in RFS between the study groups, although more tumors were detected in the PDD group (39,58).

**Progression**

There are relatively few studies that have looked at progression as an endpoint (Table III). Denzinger has compared the efficacy of 5-aminolevulinic acid (5-ALA) PDD to WLC and looked at recurrence and progression in high-grade T1 bladder tumors treated by TUR. The authors identified
46 patients with high grade T1 bladder cancer, of whom 25 were randomized to WLC and 21 to fluorescence cystoscopy. All patients underwent re-TUR using standard WLC 6 weeks after the initial resection. Adjuvant immunotherapy with bacillus Calmette–Guérin or mitomycin C was administered to most patients. At a median follow-up of more than 7 years, the RFS and the residual tumor was significantly better in the PDD group but no significant difference was observed in the rate of progression to muscle-invasive disease (59). Babjuk reported similar results with no difference in progression noted between the two modalities (14). Daniltchenko, on the other hand, did report decreased progression with PPD compared to WLC (54). It should be noted that this study used PDD at re-TUR in all patients.

### Specificity of Photodynamic Diagnosis

One of the criticisms of PDD has been the low specificity. This occurs largely because the photosensitizers are also accumulated in cells with rapid metabolic turnover, including inflammatory and infected tissue. Multiple studies have demonstrated a lower specificity of PDD (with ALA or HAL) compared to WLC (Table IV). However, three studies suggest the specificity of PDD with Hypericin to be higher than WLC (35,60-61), while other studies have demonstrated no difference (45, 62, 57). In one study, the specificity of PDD was shown to be lower than cytology; however, in the same study, PDD sensitivity was higher than the other markers tested (marker nuclear matrix protein NMP22 and cytology (63).

### Complications of Photodynamic Diagnosis

Various studies have shown the advantages of PDD, including selective tumor targeting, increased detection, and reduced toxicity allowing for repeat treatment (68, 69). The previously observed cutaneous photosensitization effect is not seen with the current intravesical agents due to decreased systemic absorption (70-72). Therefore, side effects

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**TABLE II. RECURRENCE FREE SURVIVAL: STUDIES COMPARING PDD AND WLC.**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Photosensitizer</th>
<th>RFS 12 mo WLC</th>
<th>RFS 12 mo PDD</th>
<th>RFS 24 mo WLC</th>
<th>RFS 24 mo PDD</th>
<th>RFS LATE WLC</th>
<th>RFS LATE PDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniltchenko</td>
<td>102</td>
<td>5-ALA</td>
<td>39%</td>
<td>57%</td>
<td>-</td>
<td>-</td>
<td>27% (36 mo)</td>
<td>41% (36 mo)</td>
</tr>
<tr>
<td>Babjuk</td>
<td>122</td>
<td>5-ALA</td>
<td>39%</td>
<td>66%</td>
<td>28%</td>
<td>40%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Filbeck</td>
<td>191</td>
<td>5-ALA</td>
<td>79%</td>
<td>91%</td>
<td>66%</td>
<td>90%</td>
<td>65% (36 mo)</td>
<td>85% (36 mo)</td>
</tr>
<tr>
<td>Dezinger</td>
<td>301</td>
<td>5-ALA</td>
<td>-</td>
<td>-</td>
<td>73%</td>
<td>88%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stenzl</td>
<td>402</td>
<td>HAL</td>
<td>54% (9 mo)</td>
<td>64% (9 mo)</td>
<td>-</td>
<td>-</td>
<td>64% (48 mo)</td>
<td>84% (48)</td>
</tr>
<tr>
<td>Alken</td>
<td>604</td>
<td>5-ALA</td>
<td>-</td>
<td>-</td>
<td>81%</td>
<td>82%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
and complications are usually related to the TUR. These include hematuria, urinary retention, and bladder spasms (46). Fradet et al has reported HAL related adverse events in 2.4% of patients (47). The majority of the side effects were mild to moderate. Another photosensitizer, Photofrin, has been reported to decrease bladder capacity but its use has been limited (73-75). In nearly all studies, regardless of the photosensitizer, PDD has been well tolerated with similar side effects to standard WLC (50-52).

### Photodynamic Therapeutic Effect

Along with the capability of detecting bladder tumors, a possible therapeutic effect with photodynamics has been reported termed photodynamic therapy (PDT). When Kelly et al performed the first human trials with this modality, he also reported tumor destruction within the illuminated areas (23). Several studies have proposed a theoretical mechanism of cell killing which involves the absorption of the photosensitizer and the subsequent generation of free radical species in tissues exposed to fluorescent light. This leads to activation of the inflammatory cascade and ultimately tumor death (76-78). D’Hallewin and Uchibayashi reported their experience of PDT in patients with CIS (74-79). D’Hallewin reported a 61% success rate of CIS treated with PDT at 37 months in a series of 15 patients using Photofrin II. Using 5-ALA, Burger presented PDT as an additional treatment option for recurrent NMIBC. In a series of 31 patients, 16 were free from recurrence at 2 years (80). In another small series with a follow up of 52 months, Manyak treated 34 patients with refractory diffuse urothelial carcinoma with a single instillation of Photofrin (81). This study showed a complete response in 44% of patients, a partial response in 12%, and no response in the remaining 44% at 3 months. Of the 5 patients with multiple papillary lesions 4 did not respond. Nyseo reviewed their 12-year experience in 58 patients who had failed at least one course of standard intravesical therapy to assess the long term role of PDT in the management of patients with NMIBC. Thirty-nine patients with recurrent or resistant cancer underwent PDT and 19 underwent treatment after complete resection. The overall response rate was 84% in the resistant papillary group (Ta or T1 disease), 75% in the CIS group and 90% in the intravesical naive group. The median times to recurrence and progression were 48 months and 46 months respectively, and at a median follow up of 50 months, 31 patients were free of disease. It was concluded that PDT with TUR was an effective alternative therapy for patients with refractory NMIBC and CIS (82).

More recent studies have evaluated the possibility of an increased therapeutic effect by combining PDT and chemotherapy or immunotherapy (83-84). For example, epidermal growth factor receptor (EGFR) is known to be over expressed in bladder cancer (85). Ramaswamy et al evaluated the anti-tumor effects of PDT combined with Erbitux, an angiogenesis inhibitor that targets EGFR, and reported tumor growth inhibition in a nude mouse model. They showed a statistically significant relative tumor inhibition of 93% when compared to controls (86).

The use of PDT for NMIBC has shown encouraging results and suggests that patients who have diffuse Ta or T1 bladder carcinoma or CIS refractory to standard treatment may be offered PDT before proceeding to radical surgery. This should be approached with caution as the technology is largely unproven and the consequences of delaying definitive treatment in high-grade NMIBC can be devastating. Current trials are being conducted with PDT to better define its role in the treatment of NMIBC.

### Table III. Progression Free Survival: Studies Comparing PDD to WLC

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Follow-up</th>
<th>PDD</th>
<th>WLC</th>
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<tr>
<td>Babjuk 2005</td>
<td>122</td>
<td>6-15 mo</td>
<td>91.7% (5/60 progressed)</td>
<td>91.9% (5/62 progressed)</td>
</tr>
<tr>
<td>Daniltechenko 2005</td>
<td>102</td>
<td>39-42 mo</td>
<td>92% (4/51 progressed)</td>
<td>82% (9/51 progressed)</td>
</tr>
<tr>
<td>Dezinger 2008</td>
<td>46</td>
<td>7.3-7.5 yr</td>
<td>81% (4/21 progressed)</td>
<td>88% (3/25 progressed)</td>
</tr>
</tbody>
</table>
Cost

Healthcare costs are a topic of intense debate worldwide as nations struggle to provide the best health care at a reasonable cost. The diagnosis of bladder cancer represents a significant financial burden to patients as well as the healthcare system. The main factor contributing to the high cost is the rate of recurrence and the need for a comprehensive, long-term follow up. Bladder cancer is the fifth most costly cancer in US, and the most expensive on a per patient basis (87-88). Sixty percent of the expenses are due to surgical intervention in the form of endoscopy making NMIBC the most costly subset of this disease (89,90,97). Botteman et al estimated the annual health care cost of bladder cancer from the SEER-Medicare database to be $3.4 billion in direct costs in 2001 (87). In the United Kingdom, annual costs were estimated to be $82.395 million with 60% attributed to NIMBC (90).

Because of its ability to increase detection and prolong the recurrence free survival, PDD has emerged as a new modality that may lead to overall cost reduction in treating bladder cancer. Multiple studies have examined the role of PDD in reducing the cost of TUR and found that over the mid-to-long term, there is a cost benefit. However, given the initial

### TABLE IV. SENSITIVITY AND SPECIFICITY OF DIFFERENT PRODUCTS IN PDD VERSUS CONVENTIONAL WHITE LIGHT ENDOSCOPY.

<table>
<thead>
<tr>
<th>Publication and year</th>
<th>Agent</th>
<th>Fluorescence Cystoscopy</th>
<th>White Light Endoscopy</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Kriegmair, 1996</td>
<td>ALA</td>
<td>96.9</td>
<td>66.6</td>
</tr>
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<td>Koenig, 1999</td>
<td>ALA</td>
<td>87</td>
<td>59</td>
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<tr>
<td>Fielbeck, 1999</td>
<td>ALA</td>
<td>96</td>
<td>35</td>
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<td>Riedl, 1999</td>
<td>ALA</td>
<td>94.6</td>
<td>43</td>
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<td>Al-Shukri, 2000</td>
<td>ALA</td>
<td>96</td>
<td>52</td>
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<tr>
<td>D’Hallewin, 2000</td>
<td>Hypericin</td>
<td>93</td>
<td>98.5</td>
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<td>D’Hallewin, 2002</td>
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<td>94</td>
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<td>Zaak, 2002</td>
<td>ALA</td>
<td>97</td>
<td>65</td>
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<td>Grimbergen, 2003</td>
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<td>97</td>
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<td>Sim, 2005</td>
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<td>82</td>
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<td>Hungerhuber, 2007</td>
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<td>Fradet, 2007 CIS</td>
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<td>92</td>
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<tr>
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<td>95</td>
<td>--</td>
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<tr>
<td>Ray, 2009</td>
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costs of equipment, the cost of photosensitizer and initial TUR, the upfront costs of PDD are considerably higher than WLC. Stenzl et al showed initial higher costs but demonstrated considerable savings at a three year period secondary to a 6% decrease in residual tumor (91). Another prospective study of 301 patients with NMIBC demonstrated a recurrence rate with WLC of almost twice that of PDD, with the WLC group requiring 1.2 more procedures per patient per year. The decreased recurrence rate in the PDD arm resulted in a savings of €168 per patient per year at 7 years of follow up (92). Zaak et al performed PDD in 115 patients and determined that 20 TUR procedures were avoided in 5 years of follow-up (93). According to Dindyal in a study out of the UK, a 20% decrease in the recurrence rate of newly diagnosed NIBC would save approximately £30,000 largely due to less TUR. Accounting for a reduced number of follow-up cystoscopy and decreased number of mitomycin C treatments, an approximate net savings of £45,500 per 100 new diagnoses was calculated (94). The current cost benefit studies are encouraging but the exact role of PDD in bladder cancer remains to be defined. A recent study by Malmstrom suggests that greater savings are achieved if PDD is used in high risk bladder cancer only. His study showed a first year savings of €655,000 if PDD is used in a high risk patient population, but significantly lower savings if a lower risk patient population was included (95).

**Current Recommendations of PDD in Bladder Cancer**

Different organizations and associations have recognized the role of PDD in bladder cancer. The EUA guidelines recommend fluorescence cystoscopy when CIS is a concern (14). Currently, HAL is the only photosensitizer approved for use in Europe. The Austrian Association of Urology recommends the use of PDD in two settings: patients with suspicious cytology and negative WLC and in follow-up cystoscopy for high risk urothelial carcinomas. The Canadian counterpart recently revised their guidelines for the

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**TABLE V. PHASE III CLINICAL TRIALS: DESIGN AND FINDINGS COMPARING PPD AND WLC.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Number</th>
<th>Study</th>
<th>Patient Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danlitchenko</td>
<td>102</td>
<td>Suspected NMIBC randomized, to two groups: WLC or PDD. Re-TUR with PDD in both groups.</td>
<td>Increased RFS in PPD group, Increased PFS, Decreased cost in PDD group.</td>
</tr>
<tr>
<td>Schumacher</td>
<td>300</td>
<td>Suspected NMIBC randomized to two groups: WLC or PDD, multi-centre, observer and pathologist blinded. High risk underwent 2nd TUR and BCG</td>
<td>No difference in RFS or PFS at 12 months, PDD detected more tumors.</td>
</tr>
<tr>
<td>Stenzl</td>
<td>402</td>
<td>Patients with multiple papillary or recurrent tumors randomized to WLC or WLC plus PDD, multi-centre. Follow-up cysto by WLC.</td>
<td>Improved detection and RFS at 12 months with PDD.</td>
</tr>
<tr>
<td>Alken</td>
<td>1048</td>
<td>Suspected NMIBC randomized to two groups: WLC or PDD, multi-centre. Follow-up cysto by PDD. Mitomycin C given weekly for 8 weeks in all non-pTaG1 tumors.</td>
<td>PDD increases detection of tumors, no difference in RFS because follow-up done with PDD.</td>
</tr>
<tr>
<td>Babjuk</td>
<td>122</td>
<td>Primary or recurrent tumors randomized to two groups: PDD or WLC. Follow-up cysto by WLC.</td>
<td>Improved RFS in PDD group, most significant benefit in multiple or recurrent tumors.</td>
</tr>
<tr>
<td>Penkoff</td>
<td>290</td>
<td>Randomized, multi-centre, double blinded, placebo controlled.</td>
<td>Significant increase in tumor detection with PDD, no difference in RFS at 12 months.</td>
</tr>
</tbody>
</table>
management of superficial bladder cancer and does not include PDD as an alternative diagnostic modality (June 2009). In the United States, Hexvix was only recently FDA approved.

**DISCUSSION**

Currently, high grade NMIBC remains a treatment challenge for urologists. WLC is widely regarded as the gold standard for detection and TUR. PDD may offer superiority to WLC in terms of detection, recurrence free survival and overall cost, but the current data must be scrutinized closely.

Nearly all trials comparing PDD to WLC have shown an advantage in tumor detection with photodynamics. These trials have used different study designs and treatment algorithms making direct comparisons difficult (Table V). In many of these trials, both modalities were used to examine the same bladder in a single study arm thus introducing investigator bias. In three randomized trials where a two armed approach was used, no statistical difference was found between the WLC and PDD groups either at re-TUR or in recurrence free survival (39,58,96). An increased rate of tumor detection was seen in these studies, but mainly due to the detection of CIS. Other randomized studies have shown different results. A recently presented multi-institutional, prospective, randomized study by Stenzl et al showed an advantage in RFS with PDD at 9 months while an older study showed a lasting benefit with PDD at 5 year follow-up. The different findings raise several questions regarding the actual advantage gained with PDD. First, is the increased detection gained by PDD seen in the setting of Ta or T1 lesion, or relegated to CIS? Second, does the increased detection rate correlate to altered clinical treatment and is there an overall clinical benefit to TUR performed with PDD?

In nearly all studies, an increased detection rate for CIS has been reported for PDD (Table I). While several studies reported increased detection of these tumors, others did not (see Table). In an extensive meta-analysis by Kaush et al only tumors detected by PDD in patients deemed tumor free by WLC were evaluated. Their findings showed a 20% improvement in detection of papillary lesions and a 23% increase in the detection of CIS when PDD combined with HAL or 5-ALA was used (97).

A handful of trials have looked at how PDD alters the treatment of patients. One study evaluated at patients who underwent PDD in addition to WLC and found that PDD gave additional clinical information that resulted in a change in treatment in 9% of patients. The majority of patients (17 of 27) had CIS not previously identified. CIS lesions were detected concomitantly with high grade T1 tumors in 5 patients and as a result, these patients underwent early cystectomy (55). Noteworthy in this study is that in cases of Ta grade 1-2 and T1 grade 3 tumors, no significant therapeutic change was introduced by PDD if CIS was not detected. Jocham demonstrated a significant increased detection in CIS and Ta lesions and found that overall 17% of patients received more appropriate treatment either as further postoperative procedures (10%) or more extensive intraoperative treatment (7%). The authors concluded in this study that PDD with HAL offers a statistically significant improvement in treatment over WLC in patients with bladder cancer (46). This study was unique in that it attempted to eliminate investigator bias by randomly assigning two patients per center to not undergo PDD requiring the urologist to be more thorough with WLC.

The most important question that needs to be answered if PDD is to become standard in the treatment of bladder cancer is the additional clinical benefit. As previously discussed, three randomized trials with a two arm study reported no statistical difference either at re-TUR or in RFS at either 12 or 24 months (39,58, 96). The study by Alken was confounded by the fact that all follow-up cystoscopy or TUR was performed with PDD. Also in this study, cases of “higher risk” NMIBC were treated with Mitomycin C instead of BCG making it difficult to compare these results to other studies in terms of RFS. Schumacher reported a two arm study comparing PDD with 5-ALA to WLC and showed no benefit to RFS at 12 months (58). PDD was again noted to detect more lesions than WLC in the within-patient comparison group. A randomized, double-blinded, placebo controlled trial also showed no benefit to PDD assisted TUR with RFS at 12 months (96). Stenzl et al the other hand, was able to show a benefit with PDD with improved RFS but this was not a true two armed study approach (see Table) (57). Reidl et al showed lower residual tumor rates for both Ta and T1 lesions in the PDD arm, but again each bladder was examined with each modality (56). One explanation for the increased detection rates seen in a number of these trials is simply that each bladder was scrutinized for a longer period when both modalities were employed. This would suggest that a complete TUR may be achieved with WLC if the physician would spend more time performing the initial resection. However, in two studies, RFS was shown to be improved at 5 and 8 years with PDD suggesting that PDD assisted TUR has a lasting advantage over WLC (53-54). Due to conflicting data from randomized trials, it cannot currently be stated that PDD leads to increased RFS.
Few studies have specifically looked at progression as an end-point. Of the studies that did include this in their analysis only one showed a benefit with PDD while several others did not show an advantage (Table III) (54).

**CONCLUSION**

PDD appears superior to WLC in the detection of CIS and thus may lead to better treatment strategies in these patients. However, it is unclear if PDD offers a significant advantage in detecting papillary bladder cancer. PDD may allow for a more complete TUR as indicated by lower residual tumor rate and a lower tumor recurrence rate in some studies, although randomized trials have shown conflicting results. It may be that the use of PDD can change our clinical management of re-TUR and timing of follow-up cystoscopy if improvements in initial TUR and RFS are proven, but more studies will be needed before clinical recommendations are changed. PDD at this time has not shown a benefit with progression. PDD seems cost effective compared to WLC in the long term, but this is based on reported improved RFS rates. It should be noted that this technology comes with much higher up front costs compared to WLC. The use of photodynamic therapy at this time is experimental and should be only used in clinical trials with close follow-up.

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