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Photodynamic diagnosis of non-muscle invasive bladder cancer using hexaminolevulinic acid

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Abstract

Bladder cancer (BC) is the most common tumor of the urinary tract. White light cystoscopy (WLC) is currently considered the standard investigation for diagnosis of bladder tumors. Recent studies suggest that using exogenous fluorescence (photodynamic diagnosis, PDD) can improve its diagnostic sensitivity and specificity. *Objective*: Our study aims to analyze the value of using fluorescent cystoscopy (PDD) in the diagnosis and treatment of non-muscle invasive bladder cancer (NMIBC). *Patients and Methods*: The study designed as a prospective randomized clinical trial was conducted over a 12 months period and included 44 patients with primitive NMIBC diagnosed and treated in our department in 2009. Twenty-two patients were included in the study group (PDD), while 22 patients were diagnosed and treated by conventional methods (WLC). *Results*: There were no statistically significant differences between the two groups regarding age, sex, place of origin, smoking history, clinical symptoms or presence of urological history as well as tumor size, location or number. Fluorescence cystoscopy examination identified 25.8% more tumors than the conventional examination (p=0.004). We demonstrated a significant reduction of tumor recurrence rates at 3, 6, 9 and 12 months by using PDD (HR=0.3271, 95% CI 0.1091–0.9809; p=0.0461). *Conclusions*: The use of PDD in patients with NMIBC results in significant improvement of the efficiency of their initial diagnosis cystoscopy (by over 25%). We demonstrated improved patient prognosis and quality of life following conservative TUR treatment of these tumors by significantly reducing the tumor recurrence rate (by 9–27%) in the first year of follow-up.

Keywords: bladder cancer, recurrence, photodynamic diagnosis.

Introduction

Bladder cancer (BC) is the most common tumor of the urinary tract. At diagnosis, 70% of patients with bladder cancer have superficial, non-muscle invasive bladder cancer (NMIBC) [1]. The natural evolution of bladder cancer is marked by two distinct factors: recurrence (up to 80%) that primarily affects quality of life of patients and progression to infiltration and/or metastasis (up to 15%) that affects the prognosis of these patients leading to a 10-year disease specific mortality of 4–36% [2, 3].

Pathological criteria (T-element), divide bladder tumors into non-invasive BC (Tis, Ta) and invasive BC (T1–T4). A series of clinical and prognosis criteria led to their breakup into two therapeutic groups currently widely accepted: superficial BC (Tis, Ta, T1 – non-muscle invasive bladder cancer – NMIBC) and infiltrative BC (T2–T4 muscle invasive and metastatic bladder cancer) [4].

Cystoscopy and urine cytology are the standard diagnosis methods for bladder cancer, but their sensitivity is still unsatisfactory (65%). The standard treatment for all NMIBC is the complete eradication by transurethral electroresection (TUR), a relatively simple procedure, but often incomplete, where BC recurrence or presence of residual tumor are quite common (>35%) [5]. Thus, it became obvious the need to develop diagnostic and therapeutic strategies designed to provide early diagnosis and correct management of superficial bladder tumors to reduce the recurrence rate and avoid tumor progression. White light cystoscopy (WLC) is currently considered the standard investigation for diagnosis of bladder tumors. Recent studies suggest that using exogenous fluorescence (Photodynamic diagnosis, PDD) may improve diagnostic sensitivity and specificity with an impact on the recurrence and progression rate of these tumors.

Objective

Our study aims to analyze the significance of using fluorescent cystoscopy (PDD) diagnosis and treatment of non-muscle invasive bladder cancer (NMIBC). We thus consider the possibility to improve the diagnostic accuracy of cystoscopy examination using fluorescent cystoscopy in patients with NMIBC and to increase the radicality of the treatment of these tumors by using photodynamic assisted TUR that may finally lead to a reduction in the recurrence and tumor progression rates.

Patients and Methods

The study designed as a prospective randomized clinical trial was conducted over a 12 months period and included 44 patients with primitive NMIBC diagnosed and treated in our department in 2009. Of these, 22 patients were included in the study group (PDD group), while 22 patients were diagnosed and treated by conventional methods (WLC group). Distribution of patients in both groups was conducted in a randomized single blind manner.

Patients in the PDD group received 85 mg Hexaminolevulinic Acid (HAL – Hexvix®) instillation 1–2 hours prior to cystoscopy. All patients initially underwent a cystoscopy examination followed by the resection of the tumors identified. Patients in the PDD group underwent an additional PDD cystoscopy examination with fluorescent D-Light® System (STORZ) as well as photodynamic assisted tumor resection (TUR – PDD).

Bladder biopsies were performed in selected cases from bladder mucosa areas considered suspicious at white light or PDD cystoscopy examination as well as from normal bladder mucosa.

Given the high risk of relapse and/or progression after TUR, modern treatment guidelines recommend the use of intravesical chemotherapy (Mitomycin C or Doxorubicin – Farmorubicin) within six hours after TUR for all NMIBC. These tumors were divided based on clinical and developmental study by the *European Organization for Research and Treatment of Cancer* (EORTC) in three risk categories that benefit from different adjuvant treatment strategies as recommended by the *European Association of Urology* (EAU) [6]:

- low-risk NMIBC: pTaG1 – single <3 cm, non-recurrent pTaG1/G2;
- intermediate risk NMIBC: pTaG3, pT1G1/G2 single pTaG1/G2 recurrent, multifocal;
- high-risk NMIBC: recurrent pT1, multifocal, pT1G3, Ta/T1 >3 cm, CIS.

Depending on the risk group the recommendations following TUR are: simple surveillance of the group with low risk tumors, adjuvant intravesical chemotherapy for intermediate-risk group and adjuvant intravesical immunotherapy with BCG vaccine for high-risk group [7, 8].

Accordingly, all patients included in the study underwent a postoperative chemotherapy instillation of 30–50 mg Farmorubicin within six hours after surgery and then received additional treatment according to risk group. Patients were followed by quarterly white light cystoscopy examinations for 12 months as suggested by recent studies [9].

Statistical data analysis was performed using the MS Excel and MedCalc 10.2 software.

Results

Mean patients age was 60.4 ± 9.4 years and most of them were males (sex ratio = 7/2). Smoking has been identified as a risk factor in 68.2% of patients. For 12 patients (27.2%) urological history was identified (benign prostatic hyperplasia, urethral strictures, bladder stones and chronic urinary tract infections). There were no statistically significant differences between the two study groups regarding age, sex, place of origin, smoking history and presence of urological history (Table 1).

Table 1 – ***Characteristics of the two study groups***

Category	WLC group (n=22)	PDD group (n=22)	Comments
Demographics			
Age [years]	62.09±12.46	58.77±14.31	*p*=ns
Sex ratio (B/F)	2.66	4.5	–
Urban [%]	54.5	45.4	–
Smokers [%]	72.7	63.6	–
Urological history [%]	22.7	31.8	–
Primary tumor			
No. of tumors	1.48 ± 0.73	1.66±0.94	*p*=ns
Number of tumors PDD group (*PDD *vs.* white light examination)	–	1.41±0.59 / 1.77±0.02*	*p*=0.004
Location left / right (n=)	8/5	6/6	–
Location post. / bladder trigone (n=)	4/4	5/4	–
Size [cm]	2.02±0.84	1.95±0.58	*p*=ns
Ta/T1 (n=)	6/16	4/18	–
G1/G2/G3 (n=)	7/12/3	6/14/2	–

Clinically, most patients in both groups had gross hematuria (34 cases – 77.2%; 18 in the WLC group – 81.8% and 16 in the PDD group – 72.7%) sometimes associated with lower urinary tract symptoms (frequency – 14 cases, 31.8%; dysuria – eight cases, 18.2%). In eight patients, the diagnosis was established incidentally during investigations for other pathological conditions. There were no statistically significant differences between the two groups in terms of clinical symptoms.

At the initial examination, cystoscopy identified a total of 65 tumors in both groups while PDD examination identified eight additional tumors (total 73). White light cystoscopy identified 34 tumors in the WLC group and 31 in the PDD group (1.41 ± 0.59) as well as seven cases of false positive bladder biopsies (WLC sensitivity = 79.5%). Fluorescence cystoscopy examination identified a significantly higher number of tumors in the PDD group (39 tumors, average 1.77 ± 1.02), 25.8% more than conventional examination (p=0.004). The PDD group included four cases of false positive PDD results with negative bladder biopsies and three patients with false negative PDD examination (PDD sensitivity = 92.8%). We also performed eight negative white light cystoscopy examinations and five negative PDD examinations that were not included in the study.

Average tumor size was 1.84 ± 0.57 cm (2.02 ± 0.84 cm for the WLC group and 1.95 ± 0.58 cm for the PDD group). There were no statistically significant differences between the two groups regarding tumor size, location, or their number.

In terms of the depth of invasion (T), 77% of tumors were T1 and 23% Ta. Also, regarding tumor differentiation grade 36.3% of tumors were G1, 52.3% G2 and 11.3% G3. By the EORTC risk classification, intermediate risk was the predominant category (21

patients – 47.7%) followed by the high-risk category (15 patients – 34.1%).

WLC and PDD images of bladder cancers are presented in Figures 1 and 2, showing characteristic red fluorescence of bladder tumors and blue background represented by the normal urothelial tissue under blue light PDD cystoscopy examination using the D-Light system at approximately 1–2 hours after Hexvix bladder instillation.

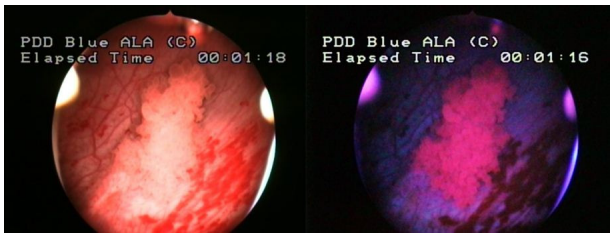

Figure 1 – ***Non-muscle invasive bladder tumor on the left side wall (white light cystoscopy – left and PDD – right) in a 60-year-old male patient (HP – moderately differentiated urothelial carcinoma with invasion of the sub-epithelial tissue – T1G2).***

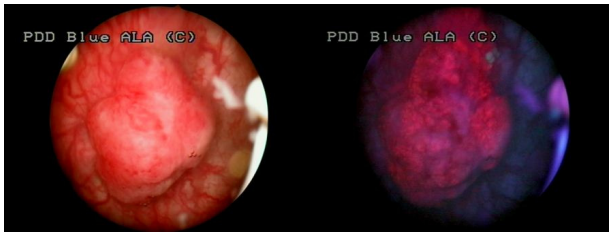

Figure 2 – ***Non-muscle invasive bladder tumor on the posterior wall (white light cystoscopy – left and PDD – right) in a 57-year-old male patient (HP – poorly differentiated urothelial carcinoma with invasion of sub-epithelial tissue – T1G3).***

Figure 3 presents a 48-year-old female patient diagnosed with T1G2 papillary tumor as well as uncharacteristic PDD positive multiple bladder nodules on the posterior-lateral right bladder wall (right) that were almost invisible under WLC examination (left). The nodules were biopsied and pathological examination showed high degree intraepithelial urothelial dysplasia (Figure 4).

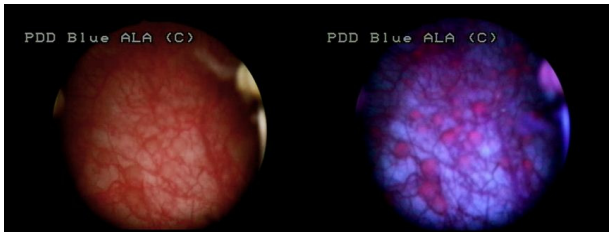

Figure 3 – ***Appearance of multiple bladder nodules on the posterior-lateral right bladder wall (white light cystoscopy – left and PDD – right) in a 48-year-old female patient (HP – urothelial high degree intra-epithelial dysplasia).***

This finding may be of crucial importance if PDD proves to be able to early detect flat urothelial lesions such as high degree premalignant dysplasia as well as carcinoma *in situ* (CIS). Unfortunately, our study group did not include any other similar lesions or CIS.

In terms of post-treatment recurrences, we identified four cases (9.09%) of patients with tumor recurrences at the first cystoscopy check performed at three months (three in the WLC group – 13.64% and one in the PDD group – 4.55%), seven cases – 15.91% at six months (five in group WLC – 22.73% and two PDD group – 9.1%), 11 patients with recurrence at nine months – 25% (eight in group WLC – 36.36% and three the PDD group – 13.64%) and 14 to 12 months of surveillance – 31.82% (10 in the WLC group – 45.45% and four PDD group – 18.18%). Noticeably the recurrence rate was decreased by 9.1%, 13.6%, 22.7% and 27.3% at 3, 6, 9, and 12 months for the PDD group (Figure 5).

Using Kaplan–Meier survival curves (Figure 6), we analyzed the recurrence-free survival rates for the two groups in a timely manner and obtained better results for the PDD group (HR=0.3271, 95% CI 0.1091–0.9809; p=0.0461), which confirmed the significant reduction of recurrence rates by using the PDD system (p=0.0408) that becomes an independent positive prognosis factor.

We identified three cases (6.8%) of tumor progression (one in the PDD group and two in the WLC group). Data was insufficient for a thorough analysis of the tumor progression rates.

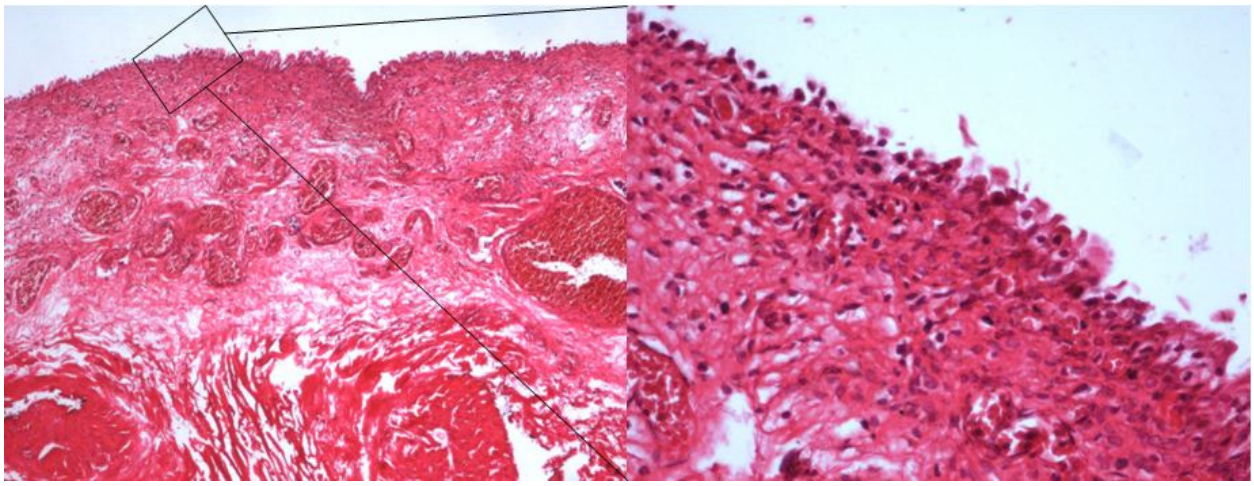

Figure 4 – ***The same patient: bladder wall with uneven, atrophic urothelium (HE stain, 40× – left); urothelial high degree intraepithelial dysplasia – detail (HE stain, 200× – right).***

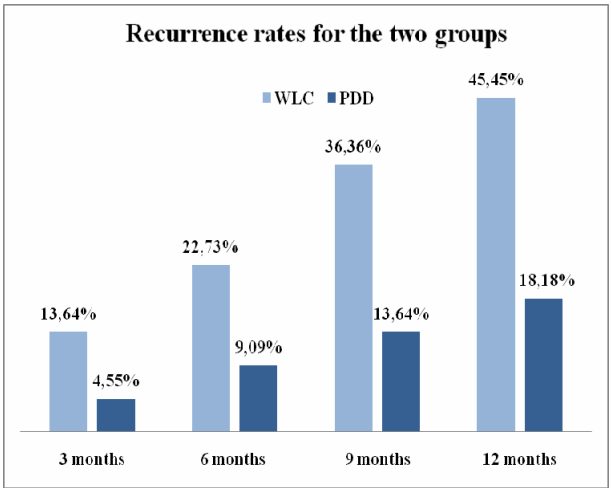

Figure 5 – ***Tumor recurrence rates for patients in the two groups at the cystoscopy controls performed in the first year of follow up (3, 6, 9, and 12 months).***

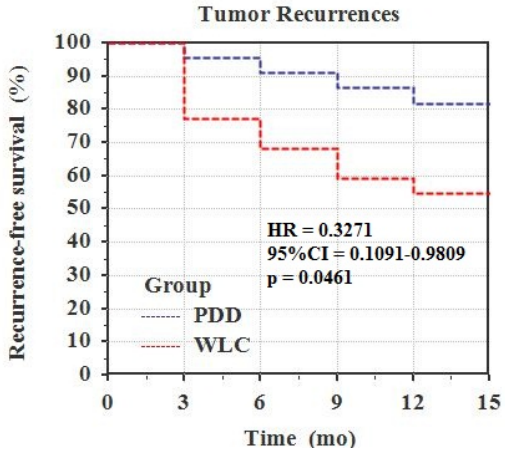

Figure 6 – ***Kaplan–Meier analysis of recurrence-free survival for the two groups during 12 months follow-up demonstrates the advantages of PDD use (p<0.05).***

Discussion

Based on a random bladder biopsies correlation model, Kriegmair M *et al.* [10] were the first who reported a significant increase in sensitivity of diagnosis of flat urothelial lesions and papillary tumors by assessing them with porphyrin-induced fluorescence using aminolevulinic acid (ALA). Specificity was up to 97% with a sensitivity of 65% comparable to white light cystoscopy (WLC). In a larger study, a Münich Group [11] reported similar values of specificity and sensitivity of 96% and 65% on a group of over 1000 patients. According to their data, 34% of tumors detected by PDD with ALA were not observed during WLC and 38.7% of tumors were high-risk group. In a later study they showed that PDD identified 30% more urothelial dysplasia lesions and 53% more CIS than WLC showing that PDD is clearly more effective than WLC in detecting flat urothelial lesions [12]. Using the new *WHO* classification of urothelial tumors (2004), many of the injuries previously considered moderate dysplasia cancers are now considered high-risk intra-epithelial carcinoma supporting the importance of increasing the rate of detection of these tumors with PDD [13] as suggested by our study as well.

At the same time, similar to our study, several studies have compared the effectiveness of PDD using HAL with the conventional white light cystoscopy (WLC). Jichlinski P *et al.* [14] reported a sensitivity of 96% (similar to ALA) compared to 73% for WLC. Another study including 211 patients with primary or recurrent bladder cancer, who received an instillation of HAL, shows that the diagnosis efficiency is increased by up to 28% compared to the WLC method. Data is similar to our findings – 25.8% increase of diagnosis efficiency.

Resection or complete destruction of all bladder tumors is considered as the main factor preventing the recurrence of bladder tumors [9]. In this context, the clinical relevance of PDD was highlighted by many authors. In prospective randomized trials, patients with clinical suspicion of bladder tumor were divided into risk groups and were treated by white light TUR or after administration of ALA. At 2–6 weeks, they underwent a new cystoscopy and TUR. Riedl CR *et al.* [15] investigated 102 such patients showing a 59% reduction in the tumor recurrence rate in patients with photo-dynamic assisted tumor resection, which was confirmed by other trials [16, 17].

To prove if the growth rate of detection of tumor lesions as well as lower residual tumor rate affects the rate of tumor recurrence, Filbeck T *et al.* [18, 19] conducted a randomized trial to compare the white light TUR and PDD assisted TUR (ALA). Patients were then followed at three months with urinary cytology and classic cystoscopy. Average follow up was 43 months for 191 patients. Recurrence-free rates at 12, 24 and 48 months were 90.9%, 90.9% and 90.85% in the PDD group and 78.6%, 69.9% and 60.7% respectively in the white light TUR group (p<0.001). PDD obvious superiority became an independent prognostic factor with an adjusted hazard rate of 0.29 between the two groups (95% CI 0.15–0.56) similar to our result (HR=0.3271, 95% CI 0.1091–0.9809; p=0.0461).

Conclusions

Use of photodynamic diagnosis (PDD) in patients with NMIBC results in significant improvement of the sensitivity and efficiency of their initial diagnosis cystoscopy (by 25%). We demonstrated improved patient prognosis and quality of life following conser-vative PDD assisted TUR treatment of these tumors by significantly reducing the tumor recurrence rate (by 9–27%) in the first year of follow-up. Our results also suggest that PDD may be able to early detect flat urothelial lesions such as high degree pre-malignant dysplasia or CIS. More complete results will obviously require including more patients in the study and having longer follow-up periods.

Abbreviations

BC – bladder cancer;
NMIBC – non-invasive bladder cancer;
WLC – white light cystoscopy;
TUR – transurethral resection;

PDD – photodynamic diagnosis;
ALA – aminolevulinic acid;
HAL – hexaminolevulinic acid;
HR – hazard ratio;
CI – confidence interval.

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