ORIGINAL PAPER

RJME
Romanian Journal of
Morphology & Embryology
http://www.rjme.ro/

Improved diagnosis and long-term recurrence rate reduction for non-muscle-invasive bladder cancer patients undergoing fluorescent hexylaminolevulinate photodynamic diagnosis

Petru Octavian Drăgoescu[1], Ştefania Tudorache[2], Andrei Ioan Drocaş[1],
George Mitroi[1], Andrei Pănuş[1], Nicoleta Alice Marilena Drăgoescu[3],
Cristian Meşină[4], Cosmin Daniel Mititelu[1], Andreea Doriana Stănculescu[3],
Guleed Mohamed[1], Paul Ioan Tomescu[1]

[1]Department of Urology, University of Medicine and Pharmacy of Craiova, Romania

[2]Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania

[3]Department of Anesthesiology and Intensive Care, University of Medicine and Pharmacy of Craiova, Romania

[4]Department of General Surgery, University of Medicine and Pharmacy of Craiova, Romania

Abstract

Background: Bladder cancer (BC) currently accounts for 5% of all malignancies and the most common tumor of the urinary tract. Diagnosis of bladder cancer is based on urine cytology and white-light cystoscopy (WLC) performed for patients with suspected bladder mass and/or hematuria. Recent studies suggest that using the fluorescence photodynamic diagnosis (PDD) significantly improves diagnostic sensitivity with a positive influence upon the recurrence rate of bladder cancer. *Objective*: To evaluate the diagnostic efficiency and long-term influence upon the tumor recurrence rate for patients with non-muscle-invasive bladder cancer (NMIBC) undergoing hexaminolevulinate PDD compared to standard WLC. *Patients, Materials and Methods*: Between 2009 and 2011, 113 primary NMIBC patients were enrolled in our prospective study and randomized in two parallel groups: 57 patients in the study group (PDD) and 56 patients in the control group (WLC). All patients had primary Ta/T1 NMIBC with good life expectancy and no significant bladder outlet obstruction [postvoid residual urine volume (PVR) <100 mL]. *Results*: Fluorescence cystoscopy examination identified 26.3% more tumors than the conventional examination (p=0.034) in the PDD group. Tumor recurrence rate analysis proved a significant reduction by up to 20% after five years of follow-up by using PDD [hazard ratio (HR) 0.566, 95% confidence interval (CI) 0.343–0.936; p=0.0267]. *Conclusions*: The use of PDD for patients with NMIBC results in a significant 26% diagnostic sensitivity improvement as well as superior patient prognosis and quality of life following conservative treatment by reducing the tumor recurrence rate with up to 20% after five years of follow-up.

Keywords: bladder cancer, hexaminolevulinate, cystoscopy, photodynamic diagnosis, recurrence.

⯐ Introduction

Bladder cancer (BC) is currently the fourth most frequent malignant disease of modern man accounting for 5% of all malignancies [1]. Males have a four times higher risk of developing bladder cancer compared to females [1]. Diagnosis of bladder cancer is based on urine cytology and cystoscopy performed for patients with suspected bladder mass and/or hematuria. Upon initial diagnosis, up to three quarters of the patients have Ta/T1 non-muscle-invasive bladder cancer (NMIBC) [2]. Standard treatment of NMIBC includes transurethral resection (TUR) of all visible tumoral tissue as well as underlying muscle followed by one immediate chemotherapy bladder instillation and various adjuvant treatment and follow-up protocols depending on tumor risk assessment (low, intermediate, high risk) [2]. Despite these well standardized diagnosis, treatment and follow-up protocols, NMIBC patients still have a high 5-year recurrence (60–80%) and progression risk (15–20%) [3]. Actually, this risk is attributed to overlooking during cystoscopy of

flat neoplastic lesions (urothelial dysplasia or carcinoma *in situ* – CIS) or even small papillary tumors as well as to the incomplete TUR of visible papillary tumors (30%). Recent studies suggest that using the fluorescence photodynamic diagnosis (PDD) significantly improves diagnostic sensitivity with a positive influence upon the recurrence rate of NMIBC.

Objective

To evaluate the diagnostic efficiency and long-term influence upon the tumor recurrence rate for patients with NMIBC undergoing hexaminolevulinate PDD compared to standard white-light cystoscopy (WLC).

⯐ Patients, Materials and Methods

Between 2009 and 2011, 113 patients with primary NMIBC were enrolled in our prospective study and randomized in two parallel groups: 57 patients in the study group (PDD) and 56 patients in the control group (WLC). Inclusion criteria were: primary Ta/T1 CIS NMIBC, over

18 years old, good life expectancy, no significant bladder outlet obstruction [postvoid residual urine volume (PVR) <100 mL].

Patients were initially diagnosed by WLC and treated by TUR of all visible tumoral tissue. Patients in the PDD group underwent an additional photodynamic cystoscopy prior to performing TUR and were than treated by photodynamic-assisted TUR at 1–2 hours after receiving a 85 mg bladder instillation of Hexvix® (Hexamino-levulinic acid – Photocure ASA, Oslo, Norway) using the fluorescent D-Light® System (STORZ). Additional bladder biopsies were performed in selected cases from bladder mucosa areas considered suspicious for papillary or flat lesions (CIS or dysplasia) at classic or PDD cystoscopy examination as well as from normal bladder mucosa. All patients received one immediate single postoperative chemotherapy bladder instillation and subsequent adjuvant treatment depending on tumor risk [simple surveillance for patients with low-risk tumors, adjuvant bladder chemotherapy for intermediate-risk patients and adjuvant bladder immunotherapy with bacillus Calmette–Guérin (BCG) vaccine or chemotherapy for high-risk patients]. Follow-up was done by WLC performed quarterly during the first two years, biannual in the third year and annual thereafter.

Tumor detection rate (inpatient comparison in the PDD group) analysis as well as tumor recurrence rate comparison as a parallel intent to treat (ITT) analysis were performed. Statistical data analysis was performed using the MedCalc software.

⌸ Results

Overall patient gender ratio was 3.5:1 (males/females), while mean age was 59.8±10 years. More than 2/3 of NMIBC patients were current or former smokers and 1/4 had previous urological history (benign prostatic hyperplasia, prostate cancer, upper urinary tract urothelial tumors, urethral stricture, etc.). Main urological symptoms were hematuria (70%) and/or lower urinary tract symptoms (LUTS) and only 12 patients were asymptomatic (10.6%). There were no statistically significant differences between the two study groups regarding gender, age, smoking habit, urological history or clinical presentation (Table 1).

Initial WLC diagnosis for the WLC group identified a total number of 92 bladder tumors for the 56 patients within the group (1.64±0.86 tumors/patient). Most patients (30 – 53.6%) had single tumors, while 26 (46.4%) cases had two or more tumors.

In the PDD group, the initial WLC identified a total number of 99 bladder tumors for the 57 patients within the group (1.74±0.99 tumors/patient), while fluorescent cystoscopy revealed 26.3% more tumors for 20 of the 57 patients (*n*=125 tumors, 2.19±1.26 tumors/patient, *p*=0.034 *vs.* WLC). PDD group included five cases of false positive PDD results with negative bladder biopsies and seven false negative PDD examinations – tumor not enhanced by PDD. PDD sensitivity was therefore 94.7%, significantly higher than WLC (79.2%). We also performed 12 negative WLC examinations and six negative PDD examinations that were not included in the study (Figure 1).

Table 1 – *General characteristics of the two groups*

Category	WLC group (*n*=56)	PDD group (*n*=57)	*p*-value
Patient data			
Age [years]	60.3±10.2	59.4±9.9	0.61[a]
Gender ratio (males/females)	3.38	3.67	ns[b]
Smokers [%]	69.6%	64.9%	ns[b]
Urological history [%]	23.2%	29.8%	ns[b]
Hematuria [%]	73.2%	66.6%	ns[b]
Primary tumor			
No. of tumors (white light)	1.64±0.86	1.74±0.99	0.59[a]
No. of tumors at the PDD examination	n/a	2.19±1.26	*0.034*[a]
Location – left/right (*n*)	12/10	11/17	ns[b]
Location – posterior wall/ bladder trigone (*n*)	16/18	13/16	ns[b]
Size [cm]	1.63±0.7	1.69±0.75	0.67[a]
Ta/T1 (*n*)	17/39	16/41	ns[b]
G1/G2/G3 (*n*)	19/30/7	22/29/6	ns[b]
CIS (*n*, %)	6 (10.5%)	3 (5.2%)	ns[b]

WLC: White-light cystoscopy; PDD: Photodynamic diagnosis; CIS: Carcinoma *in situ*; [a]Student's *t*-test; [b]Chi-squared (χ^2) test; n/a: Not available; ns: Not significant.
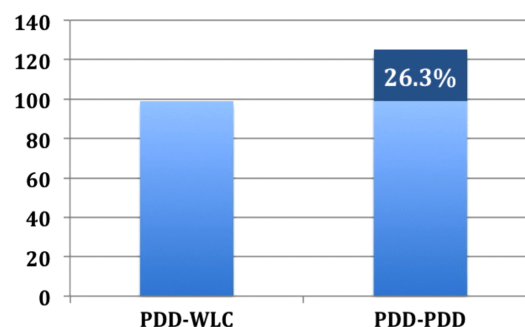

Figure 1 – *Significantly improved detection of NMIBC by fluorescence cystoscopy in the PDD group (p<0.05). NMIBC: Non-muscle-invasive bladder cancer; WLC: White-light cystoscopy; PDD: Photodynamic diagnosis.*

Tumor number ranged from one to seven, although half of the patients had single tumors only (57/113 – 50.4%), with similar distributions for both groups: 30/56 (53.6%) for the WLC group and 27/57 (47.4%) for the PDD group. However, PDD cystoscopy showed additional tumors for three single tumor patients so that the overall percentage for this group was decreased by 5% (42.1%). Average tumor size was 1.63±0.7 cm for the WLC group and 1.69±0.75 cm for the PDD group (*p*=0.67). In terms of tumor location, most tumors (50%) were diagnosed in the bladder trigone and posterior wall, while the rest were distributed between left, right and anterior walls. There were no statistically significant differences between the two groups regarding tumor size, location, or their number.

Regarding the depth of tumor invasion (T), 71% of tumors were T1 and 29% Ta, while tumor differentiation analysis identified 36% of tumors as G1, 52% G2 and 12% G3. Concomitant CIS was initially diagnosed in seven (6.2%) patients, four (7.1%) from the PDD group and three (5.2%) from the WLC group. PDD examination diagnosed two additional CIS lesions for patients undergoing fluorescent cystoscopy, increasing the CIS number to six (10.5%) (Figure 2).

Minimal follow-up period after the initial diagnosis and treatment was five years (60 months) and ranged from 60 to 83 months. Average follow-up: 72.1±6 months overall, 72.3±5.8 months for the WLC group and 71.8±6.2 months for the PDD group, with no significant differences between the two groups (p=0.64). For easier data evaluation, only the first documented tumor recurrences were considered into the study analysis. In terms of post-treatment recurrences, we identified 66 patients with recurrences in the 5-year follow-up period, so that overall 5-year NMIBC recurrence rate was 58.4%. Thirty-eight (67.9%) recurrences were diagnosed in the WLC group and 28 (49.1%) in the PDD group, so that we recorded a 19% recurrence rate reduction at the end of the study (Figure 3). Relative recurrence rate reduction between the two groups was 5.5% at the first cystoscopy (three months) and was highest at 48 months (20.5%). The overall recurrence-free survival (RFS) was 35.4 months, with a slightly longer interval for patients in the PDD group *vs.* WLC group (38.6 *vs.* 32.3 months, p=0.2) (Figure 3).
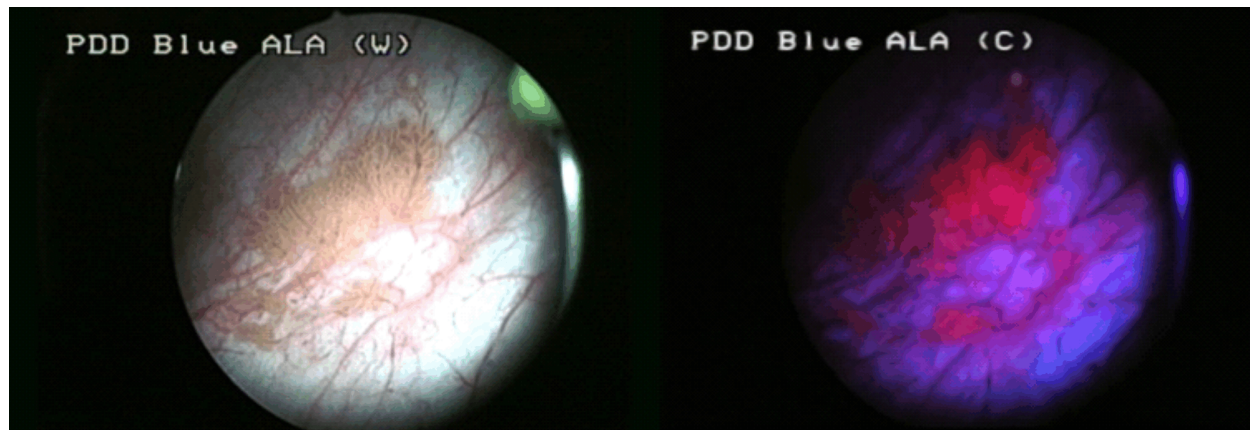
Figure 2 – *Example of a white light (W, left) and fluorescent cystoscopy examination (C, right) for a 46-year-old male patient with T1G1 NMIBC surrounded by CIS lesion. NMIBC: Non-muscle-invasive bladder cancer; CIS: Carcinoma in situ; PDD: Photodynamic diagnosis; ALA: 5-Aminolevulinic acid.*
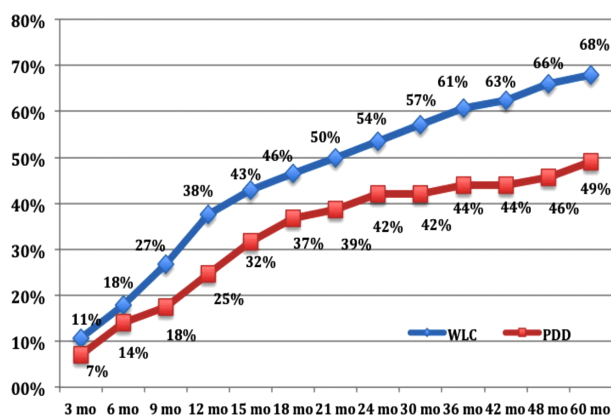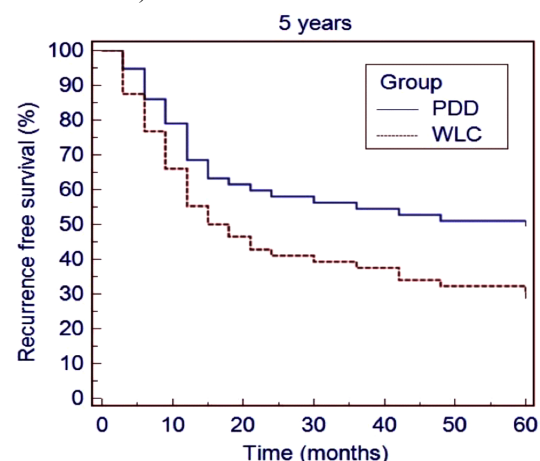

Figure 3 – *Recurrence rate comparison for the two groups at five years of follow-up. mo: Months; WLC: White-light cystoscopy; PDD: Photodynamic diagnosis.*

Using Kaplan–Meier survival curves (Figure 4), we subsequently analyzed the RFS rates for the two groups in a timely manner and confirmed better results for the PDD group [hazard ratio (HR) 0.566, 95% confidence interval (CI) 0.343–0.936; p=0.0267), which confirmed the significant reduction of recurrence rates by using the PDD method that can be therefore considered an independent positive prognosis factor for patients with NMIBC (Figure 4).

Overall tumor progression rate was 9.7% (11 patients) and 16.7% of all recurrences. There were five (8.7%) patients with tumor progression in the PDD group and six (10.7%) cases in the WLC group. Most patients (seven – 6.2%) had grade progression (G2–G3), while the rest (four patients – 3.5%) had tumor depth progression (T1–T2). However, data was insufficient for a thorough analysis of the tumor progression rates (T, G). Radical cystectomy was performed for five patients (three patients with tumor depth progression and two with high-grade recurrent tumors), three (5.2%) from the WLC group and two (3.5%) from the PDD group, respectively (p=ns). There were no cancer related deaths during the five years of follow-up, but there were two non-cancer related deaths (cardiovascular).

Figure 4 – *Kaplan–Meier recurrence free survival comparison analysis for the two groups at five years follow-up. PDD: Photodynamic diagnosis; WLC: White-light cystoscopy.*

⊟ Discussion

PDD is based on the interaction between a fluorochrome with high selectivity for cancer cells and light of a specific wavelength. Cancer tissue is subsequently observed by identifying changes in fluorescence compared to normal healthy tissue.

Since the 1960s scientists have been trying to identify new methods of cancer diagnosis using external fluorescence and various dyes (methylene blue, fluorescein and even synthetic porphyrin), but results were non-specific and the method had significant cutaneous toxicity [4–7]. Alfano *et al.* were the first to use this method *in vitro* for bladder cancer cells [8]. Later, at the beginning of the 1990s, the increasing interest for this method led to various studies using 5-aminolevulinic acid (ALA) that showed a lot of positive results in terms of tumor detection improvement and recurrence rate reduction [9–14] that were later confirmed by larger randomized trials [15, 16].

After the year 2000, hexylaminolevulinate (HAL), a new fluorochrome derived from ALA, was developed for bladder cancer diagnosis and was proved to have improved tissue penetration and cancer specificity [17, 18]. Various studies have since analyzed the value of HAL in bladder cancer diagnosis and management. Jichlinski *et al.* was among the first to report in 2003 significantly improved diagnosis sensitivity for bladder cancer using HAL, with as much as 23% [19]. His findings were subsequently confirmed by several within patient comparative trials that showed improved detection of bladder cancer by 16–29% [20–25] and even higher than 40% for CIS of the bladder [23, 26, 27]. Our study showed similar results, confirming a 26% diagnostic sensitivity improvement for patients undergoing HAL fluorescent cystoscopy. Using fluorescent cystoscopy, additional tumors were revealed for 20 of the 57 (35%) patients in the PDD group, suggesting that standard WLC misses bladder tumors in at least one in three patients leading to a higher recurrence rate.

Similar to our study, many recent randomized trials concentrated on the NMIBC recurrence rate reduction with the PDD system using HAL. Most studies, including one of our previous papers [28], confirmed the positive effect of the initial diagnostic improvement, by proving significant recurrence rate reduction between 11% and 17% at 1–2 years of follow-up [15, 29–31] that went up to 19–20% in our study, as we had a longer follow-up period (five years). A series of large multicenter meta-analyses have also been performed on HAL fluorescent cystoscopy in NMIBC and all authors proved the significant diagnosis improvement of this method, as well as significant recurrence rate reduction [32–34].

We can therefore sustain that the benefit of PDD with HAL is that if performed for four NMIBC patients, it will definitely find extratumors in at least one of them and after fluorescent-guided TUR, one additional patient out of five will be recurrence free after five years of follow-up.

The method is safe, with minimal patient discomfort, easy to perform and with practically no learning curve required for the urologist. Despite the obvious practical and oncological advantages of the method and current practice guidelines recommendation, fluorescent cystoscopy is still not used as a standard procedure. This is probably due to the price of the fluorescent substance and the endourological equipment required to perform it. However, bladder cancer is currently among the most expensive to treat cancers [35] so that the actual cost required to perform this procedure was proved to reduce the overall long-term treatment cost for bladder cancer in various countries from Europe and North America [36–40]. Decisive action is therefore required at both national and international level to include this procedure in the standard of care for NMIBC diagnosis.

Conclusions

Fluorescent HAL photodynamic diagnosis improves the diagnosis accuracy of NMIBC by 26% leading to a more complete endoscopic treatment, longer disease-free survival and up to 20% reduced tumor recurrence rate after five years of follow-up.

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Corresponding author
Ştefania Tudorache, Associate Professor, MD, PhD, Senior Obstetrics and Gynecology Specialist, Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40722–220 235, Fax +40251–502 195, e-mail: stefania.tudorache@gmail.com