DOCTORAL THESIS

ABSTRACT

EFFECT OF PHOTODYNAMIC DIAGNOSIS ON NON-MUSCLE INVASIVE BLADDER CANCER RECURRENCE AND PROGRESSION RATES

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**Keywords:** Non-Muscle Invasive Bladder Cancer, Photodynamic Diagnosis, Recurrence, Progression
A. Overview of Non-Muscle Invasive Bladder Cancer

Bladder cancer (BC) is the most frequent urinary tumors and second in line after prostate cancer among urinary tract tumors. With a global incidence of 5% of the total newly diagnosed cancers every year, bladder cancer are the fourth most frequent cancers in man after prostate, pulmonary and colonic cancer [1].

The disease is three times more frequent among man than woman and the incidence among the european caucasian population is approximately 20 new cases/year/100,000 inhabitants [1].

More than 90% of malignant tumors developed within the bladder are of epithelial origin (carcinomas) and 90% of them are (transitional) uroretial carcinomas known as “transitional cell carcinoma” (TCC) [2].

While pathologists divide bladder cancer by the T element in non-invasive BC (Tis, Ta) and invasive BC (T1-T4), a series of clinical prognosis and therapeutic criteria determined a well-known classification of BC into two groups: Superfficial or Non-Muscle Invasive Bladder Cancer - NMIBC (Tis,Ta,T1 non-muscle invasive bladder cancer) and Invasive Bladder Cancer (T2-T4 muscle invasive and metastatic bladder cancer). This classification is very useful for therapeutic reasons, as the standard treatment is represented by the transurethral resection (TUR) for superficial tumors and radical cystectomy for the invasive cancers.

At diagnosis time, 70% of the patients have non-invasive tumors (40% Ta and 30% T1). Upon presentation, 40% have G1, 25% G2, and 35% G3 tumors. Five year survival is 80% for patients with superficial cancer (Ta, T1), 55% for patients with T2 tumors, 40% for T3 and 15% for T4 [3]. Associated modern oncologic treatment may lower the recurrence rate for operated tumors by 25-30%.

The natural evolution of bladder cancer is defined by the association of two individual factors: recurrence (up to 80%) and progression towards infiltration and/or metastasis (up to 15%).

Depending on the risk for recurrence and progression, non-invasive bladder cancer is divided into three risk groups as follows [4]:

- **Low risk** group includes unique, non-recurrent pTaG1-G2 tumors;
- **Intermediate risk** group – multifocal or recurrent pTaG2 and unique, non-recurrent pTaG3 or pT1G1-G2;
- **High risk group** – multifocal or recurrent pTaG3, pT1 and pTis.

The main methods for non-invasive bladder cancer diagnosis and follow-up are cystoscopy and urine citology.
Effect of photodynamic diagnosis on non-muscle invasive bladder cancer recurrence and progression rates

Cystoscopy is usually performed under local or spinal anaesthesia with various angle telescopes which allow direct view of the bladder mucosa and pathologic lesions as well as randomized biopsy of the mucosa for early detection of microscopic tumors including carcinoma in situ (CIS). Flexible, less traumatic urethrocystoscopes have recently become available.

Urine cytology is based on the direct view of the unattached malignant cells on the urine smear. Bladder wash cytology may be used for the diagnosis of urinary epithelial cancer, patient follow-up after surgical treatment, as a screening method for high risk population and as an assessment of the biologic potential of urothelial cancer.

Standard treatment for all NMIBC is represented by complete macroscopic removal by transurethral resection (TUR) that has to include underlying muscular tissue [4]. TUR seems to be a simple procedure but, tumor recurrence or relapse are quite frequent (>35%). Therefore, due to the high risk for recurrence and/or progression after TUR, the use of intravesical adjuvant chemotherapy (Mitomicin C, Epirubicin or Doxorubicin) is recommended within the first 6 hours following the resection for all NMIBC. Depending on the risk group the recommendations are: watchful waiting and close follow-up for the low risk group, scheduled intravesical adjuvant chemotherapy for the intermediate risk group and scheduled intravesical immunotherapy with BCG vaccine for high risk tumors [5].

Final diagnosis may only be established by pathological examination of the bladder tissue obtained by cystoscopy or transurethral resection. No matter how suggestive the lesion, only microscopical examination and analysis of the tumoral cells can establish the diagnosis of bladder cancer and its accurate staging.

Patient follow-up after TUR for NMIBC consists of scheduled physical exam followed by mandatory cystoscopy ± urine cytology (every 3rd month in the first two years and than bi-annually).

B. Photodynamic Diagnosis

Limitations of the standard cystoscopy and urine cytology have become obvious once recent studies comparing white light cystoscopy (WLC) with fluorescent light cystoscopy (FLC) stated that the photodynamic diagnosis (PDD) has a higher rate of tumor detection and therefore leads to a decrease in recurrence rate following PDD guided tumor resection.

The theory of PDD is based on the interaction between a fluorochrome with high selectivity for tumoral cells and light of a certain wavelength which is absorbed by the fluorochrome and reflected at a longer wavelength. Using the fluorescence theory for bladder cancer, the
abnormal areas are identified by observing the changes in fluorescence intensity compared with the normal mucosa (which normally presents a slender degree of auto-fluorescence).

Self-fluorescence or fluorescence determined by tissue fluorochromes has been used for gathering morphological informations about tissues. Alfano et al. have been the first to describe this phenomenon in 1984 [6]. They used blue light (488nm) from an argon laser to excite tumor tissue in vitro and showed a marked decrease in tumoral bladder or prostatic tissues inoculated in mice epiderma. The downside was finding the cut-off value of the fluorescent signal that distinguishes between normal and tumoral tissue. Therefore autofluorescent techniques, though promising by not involving exogenous agents, proved to be less sensitive in clinical practice, and especially for CIS detection.

Since the 60s specialists researched in vivo methods for tumor detection using the exogenous fluorescence method and various staining agents. However, no selective staining has been achieved by using tetraciclines, metal blue fluorescein or synthetic porfirin derivates and the method has been abandoned due to the lack of sensitivity and the lasting and important cutaneous toxicity of synthetic porfirin derivates [7-10].

Later, at the beginning of the 1990s, the revived interest for the subject led to the use of the 5-aminolevulinic acid (ALA) for fluorescent detection of urotelial carcinomas. ALA is heme synthesis product and leads to the accumulation of fluorescent endogenous porfirins, especially protoporphrin IX (PPIX) in epithelial tissues. PPIX is a fluorescent metabolite with a wide excitation spectrum located around 400 nm. After bladder instillation of ALA, a selective buildup of PPIX is induced in the high proliferating tumoral tissue [11]. This determines an intense chromatic contrast between the red fluorescence of the malignant cells and the blue background of the normal mucosa upon cystoscopical examination in a certain wavelength (410 nm correspondent to the blue-violet light) [12]. The mechanisms leading to increased fluorescent PPIX production in the tumoral tissue is not yet fully uncovered, but actual theories suggest the involvement of the different metabolic rate, urotelial structure, inflammation with subsequent increase in urotelial permeability for ALA as well as the high proliferating rate of the malignant tissue with a cumulative effect [13]. However, tissue fluorescence induced by PPIX is not specific to cancer cells only as it can be identified within urotelial hyperplasia and scuamous metaplasia, inflammatory or granular tissue [14].

Due to the double layered lipid membrane of the urotelial cells, the influx of active molecules such as ALA is partly limited. Experimental studies showed that adding an ester group improves ALA penetration through biological membranes. Therefore the ALA ester derivate hexaminolevulinic acid (HAL) proved better penetration capability and improved selectivity at lower doses with a higher fluorescent effect after shorter contact time [15]. Compared to ALA,
HAL provided in an experimental study 2-4 folds higher and 2 times faster PPIX buildup at a 20 folds lower concentration [16]. Meanwhile, various studies compared PDD efficacy with HAL against that of white light cystoscopy (WLC). Jichlinski et al. [17] reported 96% sensitivity (similar with that of ALA) and only 73% for WLC. Another study including 211 primary or recurrent bladder cancer patients that received a HAL instillation showed a 28% improved efficacy compared with WLC.

As stated, PPIX buildup is not limited to malignant lesions only so that false positive results are possible. Researchers looked therefore towards identifying new photodynamic agents. Currently another fluorochrome, Hypericin, is assessed as a possible fluorescent agent for bladder cancer diagnosis. Hypericin, a hidroxilated phenantro-perilen-kinone, is found in several widely spread plants of the Hypericum gender. The most common is Hypericum perforatum (known as St. John’s wart) [18]. Its extract is widely used due to its slight antidepresive effects at a 1-2 mg daily dose, but without cutaneous photosensitivity. It is insoluble in water and determines a red fluorescence (594:642 nm) when dissolved in organic solvents [19]. Intravesical instillation of Hypericin in a murine bladder cancer model induced a 12/1 fluorescence ratio between tumoral and normal tissue [20].

D’Hallewin et al. initially investigated whether Hypericin can be used for bladder cancer diagnosis [21] within a 40 patient sample using the same PDD equipment. Their results showed 98.5% specificity and 93% sensitivity in detecting urotelial carcinoma. Subsequent data from a larger, 87 patients group showed 95% specificity and 94% sensitivity without major side effects [22]. Recently, a Hypericin based fluorescent urine cytology method with fluorescent microscopy analysis of centrifuged samples has been described [23].

Although all fluorochromes have similar sensitivity for CIS and papillary bladder cancer detection (over 90%), Hypericin proved to have the highest specificity (93%) with the possibility of significantly reducing the need for random biopsies and limiting the surgical risk. Another side of Hypericin induced fluorescence is the reduced “bleach” effect. ALA induced PPIX fluorescence the bleaching occurs after 30 minutes while no bleaching has been observed for Hypericin [22,23]. There is yet no information available regarding Hypericin tumoral affinity mechanism. Knowing that Hypericin is not metabolized by mammalian cells, its bioconversion in other fluorescent byproducts is unlikely [24].

As ALA, HAL and Hypericin are administered directly into the bladder, any potential side effect is significantly reduced [25,26], especially for Hypericin that is highly hydrophobic and not absorbable for the urotelium. Only few cases of low urinary tract symptoms were reported (urgency, dysuria) after ALA or HAL administration but those may well be induced by the urethro-vesical catheter [14,17,27].
C. Study Objectives

The study entitled "Effect of photodynamic diagnosis on non-muscle invasive bladder cancer recurrence and progression rates" aims to compare the diagnostic efficiency of white light cystoscopy (WLC) and fluorescent cystoscopy (PDD) in non-muscle invasive bladder cancer (NMIBC) patients, as well as treatment efficiency of photodynamic assisted resection and white light resection of these tumors. 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 tumor resection that may finally lead to a reduction in the recurrence and tumor progression rates.

D. Materials and methods

The study designed as a parallel prospective randomized clinical trial was conducted over a 30 months period and included 87 patients with primitive NMIBC diagnosed and treated in the Craiova Urology Department between January 2009 and June 2010. Of these, 42 patients were included in the study group (PDD group), while 45 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 identified tumors. 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 classic or PDD cystoscopy examination as well as from normal bladder mucosa. Accordingly, all patients included in the study underwent a postoperative chemotherapy instillation of 30-50 mg Farmorubicin within 6 hours after surgery and then received additional treatment according to risk group. Patients were followed by quarterly white light cystoscopy examinations for 12 months.

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

Mean patients age was $60.4 \pm 9.9$ years and most of them were males ($\text{sex ratio} = 7/2$). Smoking has been identified as a risk factor in 63.2% of patients. For 33 patients (37.9%) urological history was identified (benign prostatic hyperplasia, urethral strictures, bladder stones and chronic urinary tract infections). There were no significant differences between the two groups regarding age, sex, origin, smoking history and presence of urological history.

Clinically, most patients in both groups had gross haematuria (60 cases – 68.9%; 32 in the WLC group – 71.1% and 28 in the PDD group – 66.6%) sometimes associated with lower urinary tract symptoms ($\text{frequency} – 33$ cases – 37.9%, $\text{dysuria} – 24$ cases – 27.6%). For 4 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, laboratory or imaging findings, medical history or concomitant diseases.

At the initial examination, white light cystoscopy identified a total of 143 tumors in both groups while fluorescence examination identified 24 additional tumors ($p=0.009$, Anova test). Therefore we identified a total number of 167 tumors (confirmed by pathological examination) with an average of $1.92 \pm 1.11$ tumors/patient.

White light cystoscopy identified 73 tumors in the WLC group and 70 in the PDD group as well as 7 cases of false positive bladder biopsies ($\text{WLC sensitivity} = 74.5\%$). Fluorescence cystoscopy examination identified a significantly higher number of tumors in the PDD group (94 tumors, average $2.24 \pm 1.28$), 25.5% more than conventional examination ($p = 0.022$, Anova test). PDD group included 4 cases of false positive PDD results with negative bladder biopsies and 3 patients with false negative PDD examination ($\text{PDD sensitivity} = 96.8\%$). We also performed 8 negative white light cystoscopy examinations and 5 negative PDD examinations that were not included in the study.

Average tumor size was $1.71 \pm 0.74$ cm (1.64 ± 0.72 cm for the WLC group and 1.77 cm ± 0.76 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), 73.6% of tumors were T1 and 26.4% Ta, while regarding tumor differentiation grade 40.2% of tumors were G1, 47.1% G2 and 12.6% G3. By the EORTC risk classification, intermediate risk was the predominant category (38 patients - 43.7%) followed by the high risk category (36 patients – 41.4%). We noticed that PDD examination upgraded the risk category for 6 patients (14.3%) by diagnosing multiple tumors in patients with single tumors at the first WLC examination.
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<table>
<thead>
<tr>
<th>Category</th>
<th>WLC group (h = 22)</th>
<th>PDD group (n = 22)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>61.5±10.1</td>
<td>59.1±10.5</td>
<td>p = 0.2831 (ns)</td>
</tr>
<tr>
<td>Sex Ratio (B/F)</td>
<td>3:1</td>
<td>4:1</td>
<td>p = 0.5589 (ns)</td>
</tr>
<tr>
<td>Urban (%)</td>
<td>60</td>
<td>48</td>
<td>p = 0.3643 (ns)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>68.8</td>
<td>57.1</td>
<td>p = 0.3638 (ns)</td>
</tr>
<tr>
<td>Urological history (%)</td>
<td>42.2</td>
<td>33.1</td>
<td>p = 0.5135 (ns)</td>
</tr>
<tr>
<td><strong>Primary tumor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of tumors WLC (mean)</td>
<td>1.62 ± 0.83</td>
<td>1.67±0.93</td>
<td>p=0.847 (ns)</td>
</tr>
<tr>
<td>Number of tumors PDD (mean)</td>
<td>1.62 ± 0.83</td>
<td>1.91±1.11</td>
<td>p=0.009</td>
</tr>
<tr>
<td>Number of tumors PDD group (mean) (* PDD vs. white light examination)</td>
<td>–</td>
<td>2.24±1.28*</td>
<td>p=0.022</td>
</tr>
<tr>
<td>Location left / right (n =)</td>
<td>6/10</td>
<td>8/7</td>
<td>p=0.625 (ns)</td>
</tr>
<tr>
<td>Location ant./post./bladder trigone (n =)</td>
<td>4/15/10</td>
<td>2/11/14</td>
<td></td>
</tr>
<tr>
<td>Size (cm)</td>
<td>1.64±0.72</td>
<td>1.77±0.76</td>
<td>p=0.417 (ns)</td>
</tr>
<tr>
<td>Ta/T1 (n =)</td>
<td>14/31</td>
<td>9/33</td>
<td>p=0.602 (ns)</td>
</tr>
<tr>
<td>G1/G2/G3 (n =)</td>
<td>17/22/6</td>
<td>18/19/5</td>
<td>p=0.810 (ns)</td>
</tr>
<tr>
<td>EORTC Risk categories (n=)</td>
<td>8/22/15</td>
<td>5/16/21</td>
<td>p=0.131 (ns)</td>
</tr>
<tr>
<td>(Low/Intermediate/High)</td>
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<td></td>
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</tbody>
</table>

Table 1. Characteristics of the two study groups. (a= test Anova, c= nonparametric Chi-square test; t= Student t-test, ns = statistically nonsignificant, p > 0.05)

WLC and PDD images of bladder cancers are presented in fig. 1-3, 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.

[9]
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Figure 1. Cystoscopic image of NMIBC on the posterior bladder wall (WLC examination – left and PDD Hexvix – right) in a 47 year old male patient (Pathology – well differentiated papillary urothelial carcinoma – TaG1).

Figure 2. Cystoscopic image of NMIBC on the posterior bladder wall (WLC examination – left and PDD Hexvix – right) in a 38 year old male patient (Pathology – well differentiated urothelial carcinoma with invasion of the subepithelial connective tissue – T1G1).

Figure 3. Cystoscopic image of NMIBC on the right bladder wall (WLC examination – left and PDD Hexvix – right) in a 75 year old male patient with a concomitant T1G2 tumor (Pathology – Carcinoma in situ – CIS).
In terms of post-treatment recurrences, we identified a total number of 26 tumor recurrences in 21 patients, with a **12 months global recurrence rate of 24.1%**.

We diagnosed 8 cases (9.2%) of patients with tumor recurrences at the first cystoscopy check performed at 3 months (6 in the WLC group - 13.33% and 2 in the PDD group - 4.76%), 12 cases - 13.79% at 6 months (8 in the WLC group - 17.78% and 4 PDD group - 9.52%), 18 patients with recurrence at 9 months - 20.69% (13 in group WLC – 28.89% and 5 the PDD group – 11.90%) and 21 after 12 months of surveillance – 24.14% (15 in the WLC group – 33.33% and 6 PDD group – 14.29%).

<table>
<thead>
<tr>
<th>Group/Recurrences</th>
<th>3 mo</th>
<th>%</th>
<th>6 mo</th>
<th>%</th>
<th>9 mo</th>
<th>%</th>
<th>12 mo</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>WLC (n=45)</td>
<td>6</td>
<td>13.33%</td>
<td>8</td>
<td>17.78%</td>
<td>13</td>
<td>28.89%</td>
<td>15</td>
<td>33.33%</td>
</tr>
<tr>
<td>PDD (n=42)</td>
<td>2</td>
<td>4.76%</td>
<td>4</td>
<td>9.52%</td>
<td>5</td>
<td>11.90%</td>
<td>6</td>
<td>14.29%</td>
</tr>
<tr>
<td>Total (n=87)</td>
<td>8</td>
<td>9.20%</td>
<td>12</td>
<td>13.79%</td>
<td>18</td>
<td>20.69%</td>
<td>21</td>
<td>24.14%</td>
</tr>
<tr>
<td>Decrease</td>
<td>4</td>
<td>8.57%</td>
<td>4</td>
<td>8.25%</td>
<td>8</td>
<td>16.98%</td>
<td>9</td>
<td>19.05%</td>
</tr>
</tbody>
</table>

*Table 2. Recurrence rates for the two groups at scheduled quarterly cystoscopies*

*Figure 4. 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).*
Noticeably the recurrence rate was decreased by 8.5%, 8.3%, 17% and 19.1% at 3, 6, 9 and 12 months for the PDD group. Thus, using Kaplan-Meier survival analysis curves (Fig. 4), we assessed the recurrence-free survival rates for the two groups in a timely manner and obtained better results for the PDD group ($HR = 0.3933$, 95% CI 0.1625 – 0.9517; $p=0.0385$), which confirmed the significant reduction of recurrence rates by using PDD ($p = 0.0385$). Therefore, use of PDD becomes an *independent positive prognosis factor* that significantly reduces NMIBC recurrence by up to 20% in the first year after TUR.

We diagnosed 5 cases (5.7%) of tumor progression (2 in the PDD group and 3 in the WLC group), but no significant differences between the two groups were identified, suggesting that tumor progression rate is not particularly influenced by PDD.

**F. Discussion**

Based on a random bladder biopsies correlation model, Kriegmair et al. [28] 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 Munich group [14] 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 [29]. 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 [30].

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 et al. [17] 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 [25]. 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 et al. [26] investigated 102 such patients showing a 59% reduction in the tumor recurrence rate in patients with photodynamic assisted tumor resection, which was then confirmed by other trials [27, 31].

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 et al. [32] conducted a randomized trial to compare the white light TUR and PDD assisted TUR (ALA). Patients were then followed at 3 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).

G. Acknowledgement

This clinical study was conducted with financing from the Romanian national exploratory research project program (PCE-2), CNCSIS Project No. 1287/2008, Contract. No 1230/2009.
H. Conclusions

- **Patient age** ranged from 30 to 81 years, with an average of **60.4 ± 9.9 years**, and most of them were males (77%), with a sex ratio of 7:2.

- **Smoking** was identified as a risk factor for **63.2%** of the patients. Urologic history was identified for 38% of the patients.

- **Gross hematuria** was the main clinical finding (69%), isolated in 35 de patients (40%), or accompanied by low urinary tract symptoms (frequency, dysuria).

- Initial white light cystoscopy identified 143 tumors in both patient groups and fluorescence cystoscopy with *hexaminolevulinic acid (Hexvix®)* identified 24 more tumors in the PDD group, significantly higher than WLC (**increase of diagnostic rate 25.5%**, p<0.05).

- WLC diagnostic sensitivity was 74.5% compared to **96.8%** for fluorescent cystoscopy.

- Most frequently patients presented with tumors on the **posterior bladder wall** (30%) or **bladder trigone** (28%). In terms of the depth of invasion (T), **73.6%** of tumors were T1 and 26.4% Ta, while regarding tumor differentiation grade **40.2%** of tumors were G1, 47.1% G2 and 12.6% G3. We identified **6 cases of CIS (6.9%)** and 4 patients with intraepithelial dysplasia (4.6%).

- By the EORTC risk classification, **intermediate risk was the predominant category** (38 patients - 43.7%) followed by the high risk category (36 patients – 41.4%). We noticed that **PDD examination upgraded the risk category for 6 patients (14.3%)** by diagnosing multiple tumors in patients with single tumors at the first WLC examination.

- In terms of post-treatment recurrences, we identified a total number of 26 tumor recurrences in 21 patients, with a **12 months global recurrence rate of 24.1%**. Use of fluorescent cystoscopy and PDD assisted TUR for NMIBC led to a significant **20-30% reduction of tumor recurrence rate** for the PDD group (HR=0.2433 – 0.3933; p<0.05), so that PDD became an **independent positive prognosis factor** for these patients.

- We diagnosed **5 cases (5.7%) of tumor progression** (2 in the PDD group and 3 in the WLC group), but no significant differences between the two groups were identified, suggesting that tumor progression rate is not particularly influenced by PDD.
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Bibliography

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