Photodynamic Diagnosis of the Urinary Bladder using Flexible Instruments – Ready for the Outpatient Setting?

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Abstract

Objectives: To evaluate the feasibility and detection rate of flexible PDD cystoscopy.

Methods: In total 30 patients were included in this two-center study. A flexible endoscope and a rigid instrument were both used in the same patient. In preparation for PDD Hexylaminolevulinate was used. In every patient an experienced surgeon performed the examination of the bladder in white light and PDD using initially a rigid instrument first. Then another blinded surgeon performed a flexible cystoscopy using WL and PDD in the same patient again. In all patients a TUR-BT or bladder biopsy was performed during the same procedure.

Results: In all 30 patients flexible cystoscopy could be performed without any technical problems. In the WL setting the overall sensitivity for flexible cystoscopy were 92% (22/24) vs 83% (20/24) using the rigid endoscope. The specificity was 50% for flexible WL vs 33% for rigid WL endoscopy. The accuracy of flexible WL was higher (83%) compared to rigid (73%) cystoscopy. There was an accordance of the two methods of 83% (25/30) with a Cohen’s kappa of k=0.44 (p<0.007).

Respecting the data that were acquired in PDD mode only, there was no difference in sensitivity, specificity and accuracy between the two methods (p<0.001).

In 24/30 cases there was observed no difference between flexible and rigid cystoscopy regarding fluorescence intensity.

Conclusions: Flexible PDD using the chip on the tip technology was feasible with an excellent fluorescence quality. Sensitivity and specificity of flexible PDD was equivalent to the current gold standard - the rigid blue light endoscopy.

Keywords: Bladder cancer, flexible cystoscopy, fluorescence cystoscopy, photodynamic diagnosis, rigid cystoscopy

Introduction

The high recurrence rate of urothelial cancer as well as its challenging detection especially of aggressive tumors such as carcinoma in situ still represent one of the main challenges in bladder cancer diagnosis and treatment. To overcome this burden, different technologies have been studied and established. One of the most successful technologies regarding the direct diagnosis of tumours lesions represents the Photodynamic Diagnosis (PDD).

PDD is nowadays well established during TUR-BT and has proven a positive impact on different diagnostic levels as well as on early and late recurrence rates [1-3].

However, if we want to use PDD also in an outpatient setting, there is the clear demand for a sufficient flexible approach which guarantees patients’ comfort and a low morbidity. Unfortunately the use of flexible PDD has shown several drawbacks in the past as the diagnostic accuracy seemed not to be high enough and comparable to rigid cystoscopy.

The aim of this two-center study was to determine the diagnostic accuracy of the new generation of PDD suitable flexible cystoscopes. Therefore the new system was compared to the current gold standard for PDD – the rigid approach. Following parameters were used for comparison: clinical handling, fluorescence intensity/quality, and diagnostic accuracy.

Methods

Thirty patients with previously cystoscopically diagnosed bladder lesions were evaluated using both flexible and rigid instruments for diagnosis in white light followed by PDD. Mean age of patients was 70 years (49-87 yrs). 22% were female and 78% male (Table 1). All diagnostic examinations were performed during the procedure of TUR-BT/bladder biopsy in the operating room. A concordant setting was used in two different clinical institutions (TS, M). In each institution two experienced surgeons performed these procedures. The participating surgeons were experienced in more than 2.000 PDD
cases. In every patient one of the surgeons performed cystoscopy in white light and PDD using a rigid instrument initially. Afterwards another surgeon performed a flexible cystoscopy in white light and PDD mode again, unaware of the results of the previously performed cystoscopy. This chronological order was chosen in order to avoid impaired fluorescence intensity for the flexible approach which could have been thinkable due to a photo bleaching effect of the previous inspection of the bladder in blue light. The idea was that if flexible PDD was equally effective even after the performance of a rigid PDD, there was at least no bias against the current gold standard. The time of the performance of fluorescence endoscopy was not different between rigid and flexible cystoscopy. No photobleaching was observed during the study in the rigid or flexible PDD group of patients as time of direct blue light exposition was less than 2 minutes per lesion.

<table>
<thead>
<tr>
<th>Histology</th>
<th>%</th>
<th>n</th>
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<tbody>
<tr>
<td>No tumour</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>pTa low grade</td>
<td>47</td>
<td>14</td>
</tr>
<tr>
<td>CIS</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>pT1 high grade</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>pT2 high grade</td>
<td>10</td>
<td>3</td>
</tr>
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Table 1: Histological data of included TUR-B patients

All findings were documented on specially designed documentation sheets. (including size, shape of a tumorous lesion as well as its subjectively evaluated quality of fluorescence).

In preparation of all PDD procedures fifty millilitres of Hexylaminolevulinate (Photocure ASA, Oslo, Norway) were instillated inside the bladder for at least 60 min using a 12 French catheter. (range 65-102 min). In patients with known urinary incontinency the indwelling catheter was blocked and left inside the bladder for at least 60 min.

The used flexible endoscope had following basic characteristics: direction of view: 0°, angle of view: 120°, working length: 35 cm, instrument channel: 6,5 Charr, working instruments: 5 Charr., Sheath: 16 Charr., deflection of distal tip: 140°/210° shown in Figure 1.

Figure 1: Picture of a chip on the tip PDD suitable flexible endoscope (Storz)

The actual resection of the bladder tumours was performed under WL conditions in all cases.

Results

If we focus only on the data that were acquired using WL, the overall sensitivity for flexible cystoscopy was 92% (22/24) vs. 83% (20/24) using the rigid endoscope. The specificity was higher in flexible WL (50%) vs. 33% in rigid WL. Also the accuracy of flexible WL was higher (83%) compared with rigid WL (73 %). There was an accordance of the two methods of 83% (25/30) with a Cohen’s kappa of k=0.44 (p=0.007) (Table 2).

<table>
<thead>
<tr>
<th></th>
<th>Flexible – white light</th>
<th>Rigid – white light</th>
</tr>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>92% 22/24</td>
<td>83% 20/24</td>
</tr>
<tr>
<td>Spécificity</td>
<td>50% 3/6</td>
<td>33% 2/6</td>
</tr>
<tr>
<td>Accuracy</td>
<td>83% 25/30</td>
<td>73% 22/30</td>
</tr>
<tr>
<td>p-value</td>
<td>0.014</td>
<td>0.361</td>
</tr>
</tbody>
</table>

Table 2: Comparison of flexible white light endoscopy vs. rigid white light endoscopy: (malignant lesion only)

If we focus on the results that were acquired in PDD mode only, there was no difference in sensitivity, specificity and accuracy between the two methods (p <0.001) (Table 3).

<table>
<thead>
<tr>
<th></th>
<th>flexible - PDD</th>
<th>rigid – PDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100% 24/24</td>
<td>100% 24/24</td>
</tr>
<tr>
<td>Specifity</td>
<td>50% 3/6</td>
<td>50% 3/6</td>
</tr>
<tr>
<td>Accuracy</td>
<td>90% 27/30</td>
<td>90% 27/30</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Table 3: Comparison of flexible PDD endoscopy vs. rigid PDD endoscopy: (malignant lesions only)

The quality of fluorescence was judged by every examiner for flexible and rigid PDD. For quality assessment four different subjective levels for fluorescence (no, low, medium, high) were used. In 24 of 30 cases there was the same quality level documented for flexible and rigid PDD. This represents an accuracy of 80% (p<0.001 chi square test). No difference in quality of the fluorescence between locations of the tumor’s within the bladder (dome, side wall, etc.) was observed.

During the entire study there were observed no side effects caused by the PDD procedure or by the new flexible approach.
Discussion

The most recent metaanalysis on fluorescence endoscopy of the bladder demonstrates, that the use of PDD is associated with a significantly higher detection rate for Ta tumours (14.7%; p<0.001) and CIS lesions (40.8%; p<0.001) compared to regular white light cystoscopy. CIS was detected by PDD only, in 26.7% of cases (p<0.001). The use of PDD had a significant impact on the 12 months recurrence rate. Using PDD the recurrence rate could be lowered significantly (34.5% for PDD versus 45.4% for WL, p=0.006) [2].

These promising results in terms of tumor detection and tumor control however were acquired based on PDD examinations that were performed using rigid endoscopes only. As the advantage of PDD in terms of tumour detection and tumor treatment has been demonstrated during the last years [4-10], it seems only logical that this technology is wished to be available also in the outpatient setting. The use of flexible PDD could affect patient’s management and follow-up strategies in the future, while patients as well as our health care system could profit [11].

For the outpatient setting the actual EAU Guidelines state that „it is necessary to offer the patient the bladder examination using a flexible instrument due to patient’s comfort and morbidity“. (EAU Guidelines) The current recommendations on the use of PDD are given in different national and international guidelines and different consensus papers [1,3,12-15].

The first studies regarding PDD using flexible instruments show that flexible PDD was feasible, but unfortunately was not in 2005 the detection of bladder cancer as the regular rigid cystoscopy using PDD. Witjes and Loidl could demonstrate in 2005 that the detection rate using rigid PDD for CIS was 88%, for pTa 96% and for pT1-2 94%, whereas the rates for flexible PDD were 77%, 91%, and 91%, respectively.

However it should be mentioned that flexible PDD was still superior to regular white light cystoscopy in every case [16,17].

Witjes et al., concluded in 2005 that: „The use of flexible fluorescence endoscopy is feasible and seems to be comparable to rigid WL and slightly inferior to rigid PDD."

Today only a limited number of studies regarding this issue can be found in a literature review. Recently Bertrand et al. aimed to estimate the feasibility of a flexible videocystoscope (Wolf) in blue light using HAL for the initial diagnosis or the surveillance of bladder cancer. The objective of this study was to compare the number of lesions detected in WL and in PDD, and to further estimate the percentage of cases in which therapeutic management was changed due to PDD use. Thirty consecutive patients were included in this prospective study. The flexible cystoscopy in blue light allowed to diagnose invisible lesions in white light in three patients (10%) and has modified the treatment of five patients (16%).

Another recent Scandinavian study by Hermann et al., also aimed to evaluate PDD using flexible cystoscopes and study the diagnostic quality of biopsies for the diagnosis of non-muscle-invasive bladder cancer in the outpatient setting. Therefore in 73 patients a flexible PDD was performed. The bladder was first examined in standard white light followed by the use of PDD. The authors were able to show that PDD was superior to white light diagnosis in terms of different aspects. PDD was positive in 16 patients (22%) while WL examination was normal. Four of these patients had a positive histology for tumor (2 CIS, 2 pTa). In 20 patients (20/73, 27%) PDD identified additional tumorous lesions that were not identified in white light (5 CIS, 15 pTa). The false-positive detection rate of PDD was 0.41. False positivity was significantly reduced by simultaneous flexible biopsies disproving malignancy.

Now, eight years after the publication of these initial results on flexible PDD, new promising equipment for the performance of flexible PDD is available on the market. For our analysis we used a chip on the tip instrument by the Karl Storz Company (Tuttlingen, Germany).

Our data show that flexible PDD using this chip on the tip equipment provides at least the same information as gained using rigid endoscopes for PDD; however with an additional comfort of the flexibility of the instrument. The flexible approach seems not only useful and needed in male patients but also in female patients in order to optimize the angle to judge a fluorescent lesion the best way. Our data show that there was no difference between rigid and flexible endoscopy using PDD regarding the sensitivity and specificity of tumor detection.

Interestingly there was observed a slight advantage for flexible white light endoscopy over rigid white light endoscopy. This could be explained by an optimized inspection of the bladder wall in a flexible manner and a somehow higher magnification using the flexible instrument.

The difference in quality of the fluorescence signal in 6 of 30 patients could be explained by the individual processing of Hexylaminolevulinate within the tumor cells of patients.

A possible drawback of our study could be the fact that there was documented only one case of CIS in the presented cohort. This fact should be respected in the interpretation of the presented results. However, in the author’s opinion, it seems reasonable that CIS should be diagnosable as good as any other fluorescent lesions presented in this study. However future studies using this new approach are needed to further compare the diagnostic potential for CIS using flexible and rigid PDD suitable instruments.

To put in a nutshell, flexible PDD using the chip on the tip technology was feasible with an excellent picture and fluorescence quality. Sensitivity and specificity of flexible PDD was equivalent to the current gold standard – the rigid blue light endoscopy. There was no loss in fluorescence intensity or diagnostic information using the flexible technology. Therefore the outpatient use of a flexible PDD seems ready for diagnosis and follow-up of bladder cancer patients. However larger clinical studies need to further verify the efficiency of this new equipment in daily clinical routine.

Conflict of Interest

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

References


