Photodynamic Diagnostics and Noninvasive Bladder Cancer: Is It Cost-Effective in Long-Term Application? A Germany-Based Cost Analysis

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Abstract

Objectives: Noninvasive urothelial carcinoma of the bladder (UCB) causes an enormous economic burden to public health systems due to its life-long character and frequent recurrences. While white light (WL) cystoscopy is considered to be the gold standard for transurethral resection of the bladder, photodynamic diagnostic (PDD) has been shown to improve final outcome. Escalating healthcare costs warrant increased effectiveness in treating noninvasive UCB. No data based on assessment of costs have been published to date.

Methods: A series of 301 patients with noninvasive UCB were randomized prospectively to standard WL or PDD transurethral resections of the bladder. Intravesical adjuvant therapy was administered as reflected in the appropriate guidelines. Expenditures of subsequent procedures and PDD-associated costs were assessed.

Results: Median follow-up was 7.1 yr. Disease recurrence was found in 42% and 18% of WL and PDD patients, respectively (p = 0.0003). In the WL group 2.0 and in the PDD group 0.8 transurethral resections of the bladder were noted per patient. In the WL group 1.0 and in the PDD group 0.3 recurring UCB occurred per patient, resulting in costs of €1750 per WL patient versus €420 per PDD patient in the follow-up period, respectively. Because a single expenditure of €135 was assessed for PDD, overall costs were significantly lower (by €1195) in PDD patients. As the median follow-up was 7.1 yr, costs saved by PDD per patient per year were €168.

Conclusion: Our data suggest that PDD significantly cut costs related to recurring UCB. Further studies are needed from an economic point of view.

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1. Introduction

An estimated 90,000 urothelial carcinomas of the urinary bladder (UCBs) are expected in the European Union per year [1], and in 80% the cancer is not muscle invasive. Because up to 70% of noninvasive UCB will recur, it has a life-long character and is one of the most costly cancers from diagnosis to death [2,3]. Although data on the economics of UCB are scarce, noninvasive recurrences seem to pose the major cost. Cystectomies have been reported to account for roughly 30% and transurethral resections of the bladder (TURBs) for 40% of the expenditure [4]. Considering the yearly recurrence rate of 35% for noninvasive cases, the economic burden of noninvasive UCB is massive [5].

While white light (WL) cystoscopy is considered the gold standard for the detection of UCB and for the visualization of tumour in TURB, its sensitivity and specificity is not entirely satisfactory. Remnant tumours have been found in up to 43% at secondary resections [6]. To enhance the effectiveness of TURB, fluorescence based photodynamic methods have been evaluated since the mid-1990s. To date 5-aminolaevulinic acid is the best studied [7]. TURB guided by photodynamic diagnostic (PDD) has been reported to enhance tumour detection and reduce recurrences by 20% [8], and tumour-free survival is significantly prolonged [9,10].

Escalating healthcare costs demand evaluation of effectiveness in diagnosing and treating major malignancies. To control expenditures and increase transparency, German legislation has mandated a new remuneration system from 2007 onwards based on diagnosis-related-groups. In this system all remunerations are based on the primary diagnosis of the patient and individual disbursement (ie, duration of hospitalization) is no longer relevant [11,12].

PDD has been shown to reduce relapsing UCB while requiring additional expenditures for fluorescent agents and modified blue-light cystoscopies. Although an effective reduction in morbidity and costs by PDD has been suggested by cost estimation [13,14], no detailed economic analysis has been published to date. The aim of the present study was to evaluate whether PDD would reduce costs in comparison to WL based on a previous prospective and randomized study with a primary oncological endpoint [9].

2. Methods

2.1 Study design

Appropriate ethical and written informed consents were obtained. As described previously [9], from May 1997 to August 2000 at the Department of Urology of the University of Regensburg, 301 patients with endoscopic lesions suspicious for UCB were randomized to undergo standard WL- (n = 150) or PDD-guided TURB (n = 151). Macroscopically tumour-free resection of all lesions was obtained at TURB. To evaluate the residual tumour rate, all patients with noninvasive UCB or CIS underwent secondary WL resection of the former site of surgery 6 wk after initial surgery. Patients with muscle-invasive UCB or nonmalign histopathology were excluded from further investigation. Histopathological evaluation of all specimens was performed according to the 1994 WHO classification and the 1997 TNM system.

2.2 PDD-guided TURB

As described previously [9], patients randomized into the PDD group were given aminolaevulinic acid solution (Medac, Hamburg, Germany) by intravesical instillation. As the light source, a white light bulb with band-pass filter and xenon lamp (Karl Storz GmbH, Tuttingen, Germany) was used. Fluorescent and otherwise suspicious lesions were resected.

2.3 Adjuvant therapy

Intravesical adjuvant therapy was administered as reflected in appropriate guidelines [15]. Solitary initial pTa G1/2 UCB received no treatment, multifocal pTa/1 G1/2 UCB received mitomycin C. Bacillus Calmette-Guerin was administered in initial pTa/1 G3 UCB, CIS, or recurrences after mitomycin treatment. Recurrent pT1 G3 or CIS underwent cystectomy.

2.4 Follow-up and subsequent costs

Follow-up examinations were performed at 3-mo intervals by WL and cytology. All suspicious findings underwent WL-guided TURB; recurrences were confirmed by histopathology. Follow-up information was collected from all patients until July 2006. Cases requiring subsequent cystectomies due to UCB progressing to muscle-invasive stages were not evaluated further.

Costs for TURBs were calculated according to the ICD and diagnosis-related-groups system. A base rate of €2500 representing most hospitals was assumed; the 2006 cost-weight for UCB undergoing TURB is 0.7, resulting in €1750. Manufacturer information was obtained for calculation of PDD-related costs in the European Union. Aminolaevulinic acid (Medac) is currently distributed at €95 per instillation in Germany. Required modification of standard TURB equipment for PDD use is available at €5000 (range: €2000–7000) in Germany (eg, Olympus Deutschland GmbH, Hamburg, Germany; Karl Storz GmbH, Tuttingen, Germany; Richard Wolf GmbH, Knittlingen, Germany). To evaluate cystoscope-related costs per PDD, depreciation over 10 yr and 50 uses per year were assumed, resulting in 500 applications and €10 per use. Additional costs for single-use catheterization were €30. Thus, PDD-related cost accounted for €135 (€95 + €10 + €30).

2.5 Statistical analysis

Statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL, USA). Chi-square tests were used to
investigate statistical associations between the various parameters. Recurrence-free survival was calculated using the Kaplan-Meier method, with significance evaluated by log-rank test. For the evaluation of recurrence-free survival, patients were censored at the time of their last tumour-free clinical follow-up appointment. p values <0.05 were considered significant.

3. Results

3.1. Oncological outcome

A total of 301 patients were enrolled into the study; 103 WL and 88 PDD patients were evaluated, and 110 patients were excluded from further analysis due to nonmalignant lesions, muscle-invasive UCB, or insufficient follow-up (withdrawal from study, decline of any follow-up measurements). For patient characteristics, refer to Table 1.

The two patient groups had similar characteristics in regard to tumour stage, grade, and size (Table 1). In the WL group, there tended to be more initial diagnoses and unifocal lesions, while more patients with recurrent and multifocal disease were randomized to the PDD group. Duration of surgery was comparable: 26 min (range: 18–45 min) in the WL group and 33 min (range: 21–52 min) in the PDD group, respectively (p = 0.08). There were no major complications; minor events such as cystitis and the use of adjuvant therapy were equally distributed between both groups. Median patient follow-up was 83 mo (range: 67–104 mo) in the WL group and 86 mo (range: 66–106 mo) in the PDD group. The 7.1-yr recurrence-free survival analyzed by Kaplan-Meier (Fig. 1) revealed a statistically significant superiority of PDD (71%) compared to WL (45%; log-rank test, p = 0.0003).

In the WL group, 209 TURBs were performed due to endoscopically suspicious lesions and revealed recurring UCB as confirmed by histopathology in 99 (47%) cases. In the PDD group, 69 TURBs revealed 28 (41%) disease relapses. Thus, the ratio between malignant and nonmalignant findings did not differ between WL and PDD (p = 0.07). In PDD patients, significantly fewer subsequent TURBs (p = 0.001) and recurring UCBs (p = 0.005) were noted.

Table 1 – Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>WL group</th>
<th>PDD group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>103</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Mean patient age (yr)</td>
<td>70 (32–89)</td>
<td>68 (31–88)</td>
<td>0.09 (Fisher exact)</td>
</tr>
<tr>
<td>No. women</td>
<td>25</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>No. men</td>
<td>78</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Primary tumour diagnosis (%)</td>
<td>82</td>
<td>69</td>
<td>0.06 (chi-square test)</td>
</tr>
<tr>
<td>Tumour stage/grade (%)</td>
<td></td>
<td></td>
<td>0.75 (chi-square test)</td>
</tr>
<tr>
<td>pTa/G1</td>
<td>41</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>pTa/G2</td>
<td>28</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>pTa/G3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>pT1/G1</td>
<td>13</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>pT1/G2</td>
<td>12</td>
<td>11</td>
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</tr>
<tr>
<td>CIS</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Tumours (%)</td>
<td></td>
<td></td>
<td>0.03 (chi-square test)</td>
</tr>
<tr>
<td>Single</td>
<td>77</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Multifocal</td>
<td>23</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Prognostic risk groups</td>
<td></td>
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<tr>
<td>No. low risk</td>
<td>50</td>
<td>31</td>
<td>0.37 (chi-square test)</td>
</tr>
<tr>
<td>% no prophylaxis</td>
<td>72</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>% BCG</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>% mitomycin</td>
<td>24</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>No. intermediate risk</td>
<td>35</td>
<td>40</td>
<td>0.81 (chi-square test)</td>
</tr>
<tr>
<td>% no prophylaxis</td>
<td>17</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>% BCG</td>
<td>37</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>% mitomycin</td>
<td>46</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>No. high risk</td>
<td>18</td>
<td>17</td>
<td>0.34 (chi-square test)</td>
</tr>
<tr>
<td>% no prophylaxis</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>% BCG</td>
<td>83</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>% mitomycin</td>
<td>17</td>
<td>12</td>
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</tbody>
</table>

WL, white light; PDD, photodynamic diagnostic; CIS, carcinoma in situ; BCG, Bacillus Calmette-Guerin.
Progression of disease was identical in the WL and PDD groups, as two patients in each group developed muscle-invasive disease and had to undergo cystectomy.

3.2. Economic outcome

Because both groups underwent largely identical adjuvant and follow-up measurements and progression to muscle-invasive disease was comparable, outpatient follow-up and cystectomy-related costs were not analyzed. In the WL and PDD groups, 209 and 69 TURBs were performed in 103 and 88 patients, respectively. We noted 2.0 and 0.8 TURBs per patient, resulting in overall costs of €3500 and €1400 per patient, respectively. Disregarding TURBs with nonmalign findings (eg, inflammation), €1750 and €420 were determined as the TURB-related costs per WL and PDD patient, respectively. Subtracting PDD-related expenditures as described above (€135), TURB-related costs were still considerably lower in PDD patients, when considering all TURBs and only those revealing malignancy. Thus, TURB-related costs were less by €1330 in PDD patients, when considering all TURBs and only those revealing malignancy. Thus, TURB-related costs were less by €1330 in PDD (€1750 – €420). Then deducting €135 as the PDD-related costs, €1195 was saved per PDD patient. Because the median follow-up was 7.1 yr, costs saved by PDD per patient per year were €168 (Fig. 2).

4. Discussion

About 90,000 bladder cancers are expected in the European Union per year, and UCB poses an enormous economic stress on the medical system. The majority of costs is caused by noninvasive UCB, because it has a life-long tendency to recur in most cases [3]. The present series underlines this aspect, as 46% of all patients evaluated with noninvasive UCB had recurrence despite appropriate adjuvant therapy available during the long-term follow-up.

In 2003 the diagnosis-related-group system was introduced in Germany to compensate hospitals for inpatient procedures within the public health system, and this system will be mandatory from 2007 onwards [11,12]. Because this system allows entirely transparent determination of fees and is used to cover all expenditures related to medical procedures, it is suitable for cost analysis of the sum the public
health system is burdened with. Although marked limitations arise in transferring results beyond Germany, the present calculations may be valid with restrictions for other healthcare systems (eg, in the United States), as similar TURB-related costs have been assumed in a recent study for the United States [13]. Costs related to relapsing UCB in the median 7.1-yr follow-up period amounted to €1750 per WL case in this series. Taking current life expectancy in the European Union into account, further events of recurrences and costs have to be expected.

The major goal of medical science is to improve treatment quality. With public funding, however, economic aspects cannot be ignored. Escalating healthcare costs warrant the evaluation of methods that enhance economical treatment efficiency. In addition to disbursements related to medical procedures, UCB poses enormous additional costs on society caused by absence related to loss of productivity.

PDD based on aminolaevulinic acid has been reported to increase specificity and sensitivity of cystoscopy, improve oncological outcome by reducing recurrences by 20%, and prolong recurrence-free survival [16]. A retrospective study by Stenzl et al. suggested an improvement of treatment economics by assuming an extra 0.5 working hours related to PDD [14]. In a prospective series of 115 patients followed for a median of 40 mo, Danilchenko et al. noted lower expenditures based on cost estimation assuming an average hospital stay of 4 d [13]. However, no data based on a more exact determination of costs have been published to date.

In the present series of 191 patients followed up for a median of 7.1 yr, we compared subsequent costs of patients randomized to undergo WL- or PDD-guided TURB. We chose to restrict this analysis to TURB-related costs for two reasons. First, while muscle-invasive UCB causes enormous costs and a reduction in progression in PDD would result in consequent savings, the progression rate to muscle-invasive disease was comparable in the WL and PDD groups. Furthermore, identical adjuvant and follow-up measurements are warranted regardless of mode of visualization and were applied in both groups analyzed. In addition, follow-up cystoscopies taking place in an outpatient setting have been described to account for only 10% of expenditures, whereas the most important economic factor following initial TURB is subsequent endoscopic surgery [4,5].

As suggested by the initial evaluation of this study undertaken with an oncological endpoint [9], the long-term follow-up of the patients confirms the superiority of PDD compared to WL. PDD cases had to undergo significantly fewer TURBs for suspicious lesions and had fewer recurring UCBs. In both study groups, the ratio between suspicious lesions shown to be malign and nonmalign (ie, inflammatory) by histopathology was roughly 45% and thus comparable to previously published data [17].

Although the improved oncological outcome suggests reduced long-term costs, PDD brings with it additional costs. For this analysis, we calculated a total of PDD-related cost of €135 based on current costs in Germany. However, many factors influencing economical outcome can vary considerably. PDD equipment might be written off at a different depreciation rate, and a higher or lower volume of cases will alter costs per use. Our assumptions of depreciation over 10 yr and 50 cases annually represent a very conservative estimate, and thus costs will be considerably less in most institutions. Even if older standard equipment is modified for PDD use, PDD-related costs are not increased to a relevant level if calculated per use. Furthermore, competing products might result in different cost balances. Recent studies evaluated a potent ester of aminolaevulinic acid, Hexvix (PhotoCure ASA, Oslo, Norway) [18,19], which might provide improved outcome and is currently marketed at a different price. Furthermore, the prolonged medical attendance in relation to the use of PDD has to be taken into account. No exact analysis of this aspect was done, however, as it may vary considerably depending on institutional procedures.

Our data support the previous reports that PDD reduces costs [13,14]. In the present study, the single extra costs of €135 spent on PDD resulted in savings of €187 per patient per year in the PDD group over a follow up of more than 7 yr. When taking into account the high fraction of false-positive follow-up cystoscopies and considering TURBs for recurring UCB only, €168 per patient per year was saved.

5. Conclusions

Although the present study does not represent an exact economic analysis and the data need to be interpreted carefully due to their single-institution character and limited cases, our findings suggest that the use of PDD might result in savings. Further studies evaluating the broader use of PDD from an economic point of view are needed.

Conflicts of interest

The authors declare that no conflicts of interest exist.
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References