Blue-light cystoscopy in the evaluation of non-muscle-invasive bladder cancer

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Abstract: Bladder carcinoma is the most common malignancy of the urinary tract. Two distinct groups can be identified: non-muscle-invasive bladder carcinoma (NMIBC) and muscle-invasive bladder carcinoma. At initial resection about 75–85% of the patients will be diagnosed with NMIBC. This subgroup has a recurrence rate up to 70–80%, and a subsequent chance of disease progression. This means that patients with NMIBC require adequate treatment and thorough follow up. This high recurrence rate also means that apparently current diagnosis and treatment can be improved. It is thought that photodynamic diagnosis, by the use of a photosensitizing drug and blue-light cystoscopy, can improve the detection of tumor and therefore affect outcome for patients with NMIBC. In this paper we will discuss the role of blue-light cystoscopy in NMIBC in different aspects of the disease by reviewing the latest literature.

Keywords: non-muscle invasive bladder cancer, photodynamic, diagnosis, blue-light cystoscopy

Introduction

In the European Union, bladder carcinoma had an estimated incidence of 123,135 patients in 2012 (96,442 men and 26,693 women) [European Cancer Observatory, 2012]. In the United States the American Cancer Society estimates that 72,570 Americans will be diagnosed with bladder carcinoma in 2013 (54,610 men and 17,960 women). Over 500,000 patients in the United States are bladder cancer survivors (http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics). About three-quarters of the patients initially diagnosed with non-muscle-invasive carcinoma [Ta, T1 or carcinoma *in situ* (CIS)]. Recurrence rates in patients with non-muscle-invasive bladder cancer (NMIBC) range from 31% to 78% within 5 years from diagnosis in the low-risk and high-risk subgroups respectively. For progression of disease rates, the range is from 0.8% to 47% respectively [Sylvester *et al.* 2006]. Based on these figures, thorough follow up is advised, and often implicates lifelong evaluation. Not surprisingly, Sievert and Kruck calculated lifetime treatment costs per patient are the highest for bladder cancer [Sievert and Kruck, 2009].

Diagnosis is now a combination of urine-analysis (cytology), cystoscopy and transurethral resection of the bladder tumor (TURBT). The specificity of urine cytology can be up to 90% in experienced hands; however this is predominantly for high-grade tumors and CIS. In low-grade tumors cytology is often negative. This is reflected by the change in the 2013 European Association of Urology guideline for NMIBC, in which cytology is no longer recommended in all patients, but the role of voided urinary cytology is restricted to 'predict high grade tumor before transurethral resection' [Babjuk *et al.* 2013]. Urinary marker tests were thought to overcome the limitations of cytology, although most of them lack specificity, which makes them unsuitable for primary detection. More research has to be done in terms of performance of tests and cost effectiveness to see whether cystoscopy can be replaced by marker tests (and cytology) in the future [Babjuk *et al.* 2013].

Although Ta and T1 lesions are frequently missed on cytology, they are mostly seen on cystoscopy. However, CIS is often detected with cytology but more difficult to visualize with cystoscopy. The quality and completeness of cystoscopy with TURBT depends on different factors. First, the experience of the urologist. Brausi and colleagues demonstrated in 2001 a lower recurrence rate for

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staff urologists compared with residents or chiefs. Moreover, the use of a bladder diagram contributed to a lower recurrence rate [Brausi *et al.* 2001]. Later Brausi and colleagues reported a significant variability in recurrence rates at first follow-up cystoscopy between different institutions when they analyzed seven European Organization for Research and Treatment of Cancer trials. The recurrence rates for patients with a single tumor ranged from 0 to 20.6%, but in patients with multiple tumors this differed even more with a range from 7.4% to 45.8% [Brausi *et al.* 2002]. Based on these findings, Brausi designed a teaching program with supervised TURBT training to assess the impact of training on the outcome. This program indeed improved the quality of the TURBT by decreasing recurrence rates and complications [Brausi *et al.* 2008]. The 3-month recurrence rate fell from 28% to 16% for residents and from 8% to 3% for senior urologists. It is thought that some of the recurrences are in fact residual tumors.

Another important factor that influences the outcome of TURBT is the visibility of tumors, especially of flat lesions, CIS and low-grade tumors. The visibility is thought to be optimized by using an instillation of a photosensitizing drug in combination with blue-light cystoscopy (BLC). With the introduction of the photosensitizing drug 5-aminolevulinic acid (5-ALA) and fluorescence cystoscopy new light was shed on the diagnosis (and treatment) of NMIBC [Kriegmair *et al.* 1994]. Later, its derivate hexyl-aminolevulinate (HAL, Hexvix®, Photocure ASA, Oslo, Norway) was introduced, which seemed more practical in use. With HAL, an instillation time of only 1 h before cystoscopy is required, compared with 2–4 h for 5-ALA. In terms of efficacy, 5-ALA and HAL appeared to be equally effective in photodynamic diagnosis (PDD)-guided TURBT [Bürger *et al.* 2009]. This is the reason why studies with 5-ALA as well as HAL are grouped together in (meta-) analyses. However, since May 2010, HAL has been approved only as a compound for the detection of bladder cancer in Europe and the USA, which makes it more interesting to report on studies that specifically deal with the use of HAL.

Blue-light techniques are thought to improve tumor detection, help with an improved resection and thereby reduce residual tumor. Jichlinski and Leisinger, for example, estimated that 10–20% of tumors are missed with standard white-light cystoscopy (WLC) [Jichlinski and Leisinger, 2005], and as stated above, in certain subgroups of patients this can be as high as 45% [Brausi *et al.* 2002]. The consequences of better detection on the outcome of patients with NMIBC are discussed in this article. Some studies found a prolonged recurrence-free survival (RFS) in patients in whom BLC was performed [Daniltchenko *et al.* 2005; Riedl *et al.* 2001; Zaak *et al.* 2001]. However, some conflicting data were published on the value of BLC. For example, in a prospective, randomized multicenter trial by Schumacher and colleagues published in 2009, no significant difference was found on RFS or progression-free survival (PFS) comparing fluorescence-guided cystoscopy with 5-ALA *versus* WLC [Schumacher *et al.* 2010]. Below an overview is given of the literature on PDD. To address this controversy, we reviewed data of two meta-analyses [Kausch *et al.* 2010; Shen *et al.* 2012] completed with the data of randomized, prospective studies published after April 2011. During this writing process a new meta-analysis by Bürger and colleagues was published, which seems to have more clinical relevance than the other meta-analyses, as it is the first meta-analysis discussing the results of prospective studies only using HAL as the photosensitizing drug, instead of analyzing data from studies that used 5-ALA or HAL. Because of the chosen study design, raw study data instead of published data were used, these results seem to give a more accurate picture on the value of BLC with HAL [Bürger *et al.* 2013].

Photodynamic diagnosis: the technique

In PDD two photosensitizing drugs are used: 5-ALA and HAL. The latter is a derivate of 5-ALA and seems to be superior in use in that it needs a shorter instillation time, is more stable in white light, has a better fluorescence intensity and has a more homogeneous enhancement and distribution in photoactive porphyrins [Jichlinski *et al.* 1997; Marti *et al.* 2003]. After instillation, the drug is actively transported into the urothelial cytoplasm and incorporated in the conventional cellular hem-biosynthesis metabolism. Cellular enzymatic abnormalities, as present in cancer cells and precancerous tissue, lead to accumulation of protoporphyrin IX (photoactive porphyrins). The drug is eliminated in normal urothelial tissue. By illuminating the bladder wall with blue light (380–450 nm) the porphyrins in abnormal cells emit red fluorescence; normal cells appear blue green. This improves differentiation between benign and malignant tissue and will identify the

borders of tumor more accurately [Jichlinski and Jacqmin, 2008].

Tumor detection

Detection of non-muscle-invasive bladder carcinoma

In the meta-analysis by Kausch and colleagues, data were collected from prospective studies comparing WLC with BLC from 1999 to 2008. The primary diagnostic endpoint of the meta-analysis was additional detection rate of tumor, which is determined by the number of additional tumors found when BLC is added to WLC. Because of great heterogeneity in the studies, they combined all entities of papillary non-muscle-invasive tumors in their analysis; CIS was calculated separately. For additional detection rates of all non-muscle-invasive tumors, seven studies were included, analyzing a total of 900 patients [Kausch *et al.* 2010]. The additional detection rates ranged from 5% to 49%, with a random effects estimate of 20% [95% confidence interval (CI) 8–35%)] Shen and colleagues in their meta-analysis claimed to have reviewed 14 randomized, controlled trials (from 2001 to April 2011) [Shen *et al.* 2012]. In nine of 14 studies they did not find significant higher detection rates in the BLC group, with a total tumor detection rate of 91.8% (1569/1710 patients) *versus* 90.0% (1383/1522 patients) in the WLC group ($p = 0.64$). Both meta-analyses included trials with the use of either 5-ALA or HAL. The recently published meta-analysis by Bürger and colleagues included 10 prospective studies to assess the value of BLC (using HAL as the photosensitizing drug) by collecting raw data from the separate studies and putting them into one database (literature search in July 2011). They were able to assess detection rates on a patient level as well as on a tumor level. In this study, subgroup analyses were performed per tumor type and different risk profiles. Additional detection rates for Ta tumors ranged from 9.7% to 40.2% with BLC. Moreover, 14.7% (239/1621) of Ta tumors were only detected by BLC [$p < 0.001$; odds ratio (OR) 4.989; 95%CI 1.937–12.390]. For T1 tumors additional detection rates ranged from 3.6% to 54.5%, with 10.8% (40/372) detected only by BLC ($p = 0.050$; OR 2.253; 95% CI 0.999–5.081 [Bürger *et al.* 2013]. More recent prospective studies also found additional tumors in 49% (44/90 patients) [Hermann *et al.* 2011] and 35.2% (50/142 patients) [Geavlete *et al.* 2012] with BLC.

Detection of carcinoma in situ

A previous review and additional studies described the benefit of BLC over WLC in the detection of NMIBC, which seemed to be particularly remarkable for CIS with a 20% higher detection rate [Witjes *et al.* 2010]. Kausch and colleagues also found increased detection for CIS. Data were extracted from seven studies, which comprised a total of 219 patients with CIS. Additional detection rates ranged from 17% to 78% and a random effects estimate of 39% for CIS (95% CI 23–57%). However, two out of seven studies were thought to have selection bias and therefore a separate analysis was done without these two studies. This resulted in an additional detection rate of 23%, comparable with previous data. In contrast, Shen and colleagues did not find a significant difference in detection of CIS between the two groups, although there was a clear trend in their analysis (relative risk (RR) 0.82; 95% CI 0.67–1.02; $p = 0.07$) [Shen *et al.* 2012]. More recent literature is consistent in showing significant better detection rates for CIS; for example, a detection rate for CIS of 94.3% for BLC *versus* 62.9% for WLC ($p < 0.001$) [Geavlete *et al.* 2012]. The meta-analysis of Bürger confirms a highly significant additional detection rate for CIS lesions ranging from 31.9% to 70.6% ($p < 0.001$). Moreover 48% (215/527) of the CIS lesions were found only by BLC (OR 12.372; 95% CI 6.343–24.133; $p < 0.001$) [Bürger *et al.* 2013].

Residual tumor

In some studies residual tumor rates are also given. This is tumor visible at a second resection, which is thought not to have been removed completely at the initial TURBT. Residual tumor rate in the aforementioned meta-analyses by Kausch and Shen and colleagues is defined as histologic evidence of tumor at second resection from 10 days to 6 weeks after the initial TURBT. Kausch and colleagues extracted data from three trials with a total of 394 patients. All three studies compared white light plus blue light at initial resection *versus* white light only. For the second resection, one of the studies used blue light as well, whereas two trials performed the second resection under white light. They demonstrated residual tumor rates in the BLC group ranging from 4.5% to 32.7% *versus* 25.2–53.1% in the WLC group. The random effects OR for residual tumor was 0.28 (95% CI 0.15–0.52) [Kausch *et al.* 2010]. Shen and colleagues also showed a significant

advantage, with a RR for residual tumor that was 2.77-fold higher (95% CI 1.47–5.02; $p = 0.002$) in the WLC group (863 patients) compared with the BLC group (743 patients) [Shen *et al*. 2012].

In conclusion, with the use of BLC at initial TURBT bladder tumors in general are detected better, which is especially true for CIS. This is thought to give less residual tumor, which could in turn affect treatment strategy.

Changes in treatment due to detection

The importance of a complete resection and the consequences for further treatment is outlined by Jocham and colleagues. In a comparative, within-patient, controlled study (146 patients) they recorded the differences in recommended treatment after either BLC- or WLC-guided TURBT. Due to improved detection, about 20% of patients received more appropriate treatment [Jocham *et al.* 2005]. Geavlete and colleagues also found that in the BLC group postoperative treatment changed in 19% of the patients compared with 6.3% in the WLC group ($p < 0.001$). In the BLC group this meant that 4.2% would have received chemotherapeutic instillation and another 7.7% would receive bacillus Calmette-Guérin (BCG) instillations, instead of these patients receiving no adjuvant therapy at all. This is a significant difference of 0.7% and 1.4% respectively ($p = 0.001$ and $p < 0.001$ respectively) compared with the WLC group [Geavlete *et al.* 2012]. One can imagine that these altered strategies in turn could affect recurrence and survival rates.

Disease recurrence, recurrence-free survival, time to recurrence

In their meta-analysis, Kausch and colleagues included three trials with 415 patients for data on RFS and found that at 12 months, RFS was 15.8–27% higher in the BLC group and 12–15% higher at 24 months than in the WLC group (combined $p = 0.00002$) [Kausch *et al*. 2010]. In contrast, on pooling data for RFS at 3 months from three trials with 212 patients, Shen and colleagues found no significant difference between the two groups (RR 1.15; 95% CI 0.79–1.66; $p = 0.46$). At 12 months RFS could be calculated from eight studies with a total of 1116 patients and this also did not show significant differences (RR 0.86; 95% CI 0.70–1.06; $p = 0.16$) [Shen *et al*. 2012]. The Bürger analysis on HAL BLC did show significantly lower recurrence rates 12 months postoperatively in favor of BLC (34.5% *versus* 45.4%; $p = 0.006$; RR 0.761; 95% CI 0.627–0.924) [Bürger *et al*. 2009]. Some prospective smaller trials also found significantly higher recurrence-free rates at 12 months of follow up [Hermann *et al.* 2011; Geavlete *et al.* 2012; Karaolides *et al.* 2012]. For example, Hermann and colleagues found a RFS of 30.5% (18/59) for BLC *versus* 47.3% (35/47) for WLC at 12 months ($p = 0.05$).

There are few data for 1-year follow up. Geavlete and colleagues found significantly lower recurrence rates at 24 months for BLC [21.6% (27/125) *versus* 32.5% (37/114); $p = 0.005$] [Geavlete *et al.* 2012]. More recently, Grossmann and colleagues reported on a study extension protocol for their prior multicenter, prospective, randomized trial [Stenzl *et al.* 2010] which led to long-term follow up of 255 patients in the PDD group (median follow up 55.1 months) and 261 from the WLC group (median follow up 53.0 months) [Grossman *et al.* 2012]. Median RFS in the BLC group was 16.4 months *versus* 9.6 months in the WLC group ($p = 0.04$).

Median time to recurrence ranged from 12 to 17 months in BLC groups *versus* 5–8 months in WLC groups [Kausch *et al.* 2010]. Karaolides and colleagues found comparable results with a median time to first recurrence from 13.6 months for fluorescence-guided cystoscopy ($N = 41$; median follow up 17.5 months; range 6–25) compared with 7.0 months ($p < 0.001$) for WLC ($N = 45$; median follow up 14 months; range 4.5–25) [Karaolides *et al.* 2012]. In terms of time to recurrence, no significant difference was found between BLC and WLC in Bürger's meta-analysis [Bürger *et al*. 2013].

It can be concluded that BLC seems to reduce recurrence rates for at least 1 year. Consequently RFS and median time to recurrence are prolonged.

False-positive rates, sensitivity, specificity

In eight studies from Kausch's meta-analysis, false-positive detection rates on lesion basis were higher in the BLC group except for one study. Shen and colleagues found false-positive rates of 26.3% (139/529) in the BLC group, which was 17.3% (60/347) in the WLC group (RR 0.69; 95% CI 0.49–0.97; $p = 0.03$). Surprisingly, they describe this difference as not significant. In more

recent literature no significant difference is found, with false-positive rates for BLC ranging from 14.7% to 36.5% *versus* 11.6–45.1% in the WLC groups (p = 0.052 and p = 0.445 respectively) [Geavlete *et al.* 2012; Lapini *et al.* 2012].

False positivity can be caused by inflammation, recent BCG instillation (<12 weeks) and by a recent transurethral resection itself. Ray and colleagues, for example, described a false-positive rate of 64% in patients treated with BCG instillations [Ray *et al.* 2007]. To lower false-positive rates, Draga and colleagues recommend postponing a second TURBT by 9–12 weeks after prior TURBT or BCG instillation [Draga *et al.* 2010]. A meta-analysis by Lerner and colleagues who analyzed three multicenter trials reported a significantly lower probability of detection of CIS in BLC groups treated with chemotherapy or immunotherapy instillations [Lerner *et al.* 2012]. This could be due to a better initial TURBT with BLC compared with WLC, but another suggestion is that an inflammatory response to intravesical therapy can make detection by BLC more challenging and therefore influences detection rates. False-positivity rates for detection of CIS from three multicenter prospective phase III studies demonstrated the following rates; 13% *versus* 10% [Schmidbauer *et al.* 2004], 39% *versus* 31% [Fradet *et al.* 2007] and 37% *versus* 26% [Jocham *et al.* 2005] for HAL-guided cystoscopy and WLC respectively. This shows that the differences between groups are limited. Finally, false-positive detection rates seem to decline with experience as is demonstrated by Mynderse and colleagues, with only 12% false-positive rate for HAL *versus* 11% for WLC in 2009 [Mynderse *et al.* 2009].

Even more important than false-positive rates are sensitivity and specificity of a diagnostic procedure because this is of relevance for further treatment. In terms of sensitivity, Lapini and colleagues found significantly higher sensitivity in analyzing 234 suspicious lesions with fluorescence-guided cystoscopy (99.1%) compared with WLC (76.8%; p < 0.00001) [Lapini *et al.* 2012]. Specificity was not significantly different (36.5% *versus* 30.2% respectively; p = 0.445). Similar results were reported by Lee and colleagues who looked at 134 specimens extracted under white and blue light. Sensitivity for BLC was 92.3% *versus* 80.8% for WLC (p = 0.021). Specificity was not significantly different: 48% for the BLC group *versus* 49.1% for the WLC group (p > 0.05) [Lee *et al.* 2012]. These sensitivity scores are promising and show significant advantage of BLC added to WLC in detecting tumors and therefore seems to be of value in the diagnosis of NMIBC. In addition to other diagnostic tools a more accurate diagnosis can be made.

Progression to muscle-invasive bladder carcinoma

Kausch and colleagues could not use the data of all studies for a meta-analysis on progression of disease because of missing data in three separate studies [Kausch *et al.* 2010]. Daniltchenko and colleagues found significantly less progression to muscle-invasive disease their BLC group (82% in BLC *versus* 92% in WLC) [Daniltchenko *et al.* 2005]. Babjuk and Denzinger and colleagues found no differences between the two groups [Babjuk *et al.* 2005; Denzinger *et al.* 2008]. The meta-analysis by Shen and colleagues reported no significant difference in PFS rates at 12 months (RR 0.99; 95% CI 0.94–1.04; p = 0.57) and 24 months (RR 1.02; 95% CI 0.98–1.06; p = 0.35) after initial TURBT [Shen *et al.* 2012]. PFS rates on long-term follow up at 5, 7.5 and 8 years appeared to be similar in both groups in studies by Danilchenko and Denzinger and colleagues [Daniltchenko *et al.* 2005; Denzinger *et al.* 2007, 2008]. The meta-analysis by Bürger and colleagues could not report on disease progression [Bürger *et al.* 2013].

In a prospective randomized study with 362 patients progression rates did not differ significantly: 2.4% in HAL-guided cystoscopy *versus* 4.4% in WLC at 1 year (p = 0.195). At 2 years of follow up the rates were 4% *versus* 7% (p = 0.123) [Geavlete *et al.* 2012]. Similarly, Grossmann and colleagues found a trend towards improvement of tumor-free survival and bladder preservation. With a median follow up of 55.1 months in the BLC group and 53.0 months in the WLC group, they found that at first recurrence, six patients (2.4%) in the BLC group had a T2–T4 tumor *versus* nine patients (3.5%) in the WLC group. Overall 8 patients (3.1%) in the BLC group and 16 patients (6.1%) in the WLC group developed T2–T4 tumors (p = 0.066). A cystectomy was performed in 4.8% (13/271) and 7.9% (22/280) respectively (p = 0.16) [Grossman *et al.* 2012]. No statistical significance was reached because power calculations were not performed for these parameters in the study extension protocol.

In conclusion, it looks like there is a trend for prolonged PFS in patients diagnosed with BLC.

More research has to be done with adequate long-term follow up and adjustment for the effect of additional treatment with bladder instillations. Preferably, also subanalyses should be done with different tumor grades.

Safety and costs

As mentioned before, bladder cancer has the highest lifetime treatment costs per patient of all cancers [Miller *et al.* 1996]. High costs are mainly based on the surveillance costs and treatment with TURBT and bladder instillations. However, calculations on costs of bladder cancer are difficult to assess and compare due to differences in healthcare systems, treatment reimbursements and guideline diligence. As BLC gives higher detection rates and more complete resections it is thought that it can be cost effective. Furthermore, with BLC affecting RFS rates, costs could be saved by reducing the number of follow-up cystoscopies and increasing the interval between them. Therefore, Sievert and colleagues concluded that BLC gives a long-term cost benefit, although initially higher costs are made [Sievert *et al.* 2009].

In Sweden in 2009, Malmström and colleagues designed an analytic model to estimate the budget impact of the use of PDD on the Swedish health service [Malmström *et al.* 2009]. They found a reduction in costs for the use of BLC in all newly diagnosed patients with NMIBC. In their model, patient stratification was based on the risk of tumor recurrence and progression in accordance with European Association of Urology guidelines on bladder cancer, adjusted to Swedish clinical practice. Follow up was only for 1 year following initial TURBT. In the case of tumor recurrence, the follow-up TURBT was performed with BLC as well.

Recently a trial by Garfield and colleagues looked at safety and cost effectiveness in the USA [Garfield *et al.* 2013]. They compared the use of blue light in addition to white light at initial TURBT *versus* WLC only. Follow up was performed with WLC only. For their analysis they mainly used estimates from the Grossman publication [Grossman *et al.* 2012]. Three potential outcomes were assumed for the model: recurrence monitoring for patients with proven NMIBC; ongoing monitoring for patients in whom no bladder cancer was found; and muscle-invasive surveillance for patients diagnosed and treated for MIBC. They also found a 15% reduction in costs in 4.5 years of follow up. Looking at utility estimates, they found an 11% improvement for the BLC group, meaning that these patients avoid higher cancer burden for recurrent or progressive disease in their follow up. Costs associated with side effects and purchase of equipment were not considered in this study.

In conclusion, the use of BLC seems cost effective, but no prospective data are available. Retrospective calculations and models using data from randomized, controlled trials are hampered by the differences in healthcare systems, treatment reimbursements and compliance with guidelines.

In terms of safety, studies only report mild adverse events. No phototoxicity is observed and most adverse events are mild and seem to be related to the tumor and the resection rather than to the photosensitizing drug [Hermann *et al.* 2011; Geavlete *et al.* 2012; Lapini *et al.* 2012]. Frequently mentioned adverse events are bladder pain, bladder spasm, dysuria and hematuria.

Discussion

To summarize, the results of the two meta-analyses [Kausch *et al.* 2010; Shen *et al.* 2012] differ on some points. Whereas Kausch and colleagues see better detection rates and increase in tumor-free survival, no significant differences are found by Shen and colleagues. Differences in results could be due to heterogeneity in protocols (e.g. the correct use of the photosensitizing drug and different treatment strategies after TURBT). Furthermore, Shen and colleagues used datasets twice (references 15 and 19 in their article) and included one retrospective study in their analysis (reference 12 in their article). Both analyses do agree in terms of significant reduction in residual tumor. A limitation of both analyses is the fact that they included data from studies with 5-ALA as well as HAL. Although Bürger and colleagues did not find a difference in recurrence rates or residual tumor rates between 5-ALA and HAL [Bürger *et al.* 2009], there are pharmacological advantages for HAL [Jichlinski *et al.* 1997; Marti *et al.* 2003]. For example, one can imagine that the shorter instillation time for HAL is better for protocol diligence, which will influence outcome positively. As HAL is the only approved photosensitizing drug, it seems reasonable to collect data on studies with HAL only, as was done by Bürger and

colleagues recently [Bürger *et al.* 2013]. Using original raw study data as opposed to published data, they were able to show significant additional tumor rates in BLC. More specifically, 24.9% ($p< 0.001$) of Ta and T1 tumors and 26.7% ($p < 0.001$) of CIS tumors were missed with WLC. This has great consequences for decisions on treatment strategies. Also, with regard to recurrence rates, this meta-analysis showed significant reduction in BLC of 11% ($p = 0.006$; RR 0.761). The results of this recent meta-analysis by Bürger and colleagues are supported by some recent prospective studies. No conclusions could be drawn by Bürger's analysis on time to recurrence or on disease progression. Data on disease progression are lacking in most studies, although a recent prospective study by Karaolides and colleagues found a trend for reduced progression of disease after BLC [Karaolides *et al.* 2012].

Conclusion

It seems that BLC is of benefit in all initial TURBT in decreasing the rate of residual tumor, and of special benefit in the diagnosis of CIS. For now, however, the updated European guideline recommends the use of BLC in patients who are suspected of harboring a high-grade tumor, for example, for biopsy guidance in patients with positive cytology or with history of high-grade tumor. Especially when centers already have experience and expertise and the right equipment is available, BLC could support diagnosis in certain cases. Prospective, randomized future studies could add to the discussion of the benefit of BLC, especially the impact BLC can have on progression and survival and overall costs for healthcare in patients with NMIBC.

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Conflict of interest statement

J.A. Witjes is an advisor for Ipsen.

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