



Bladder Cancer

Transurethral Resection of Non–Muscle-Invasive Bladder Transitional Cell Cancers With or Without 5-Aminolevulinic Acid Under Visible and Fluorescent Light: Results of a Prospective, Randomised, Multicentre Study

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Abstract

Background: Fluorescent light (FL)–guided cystoscopy induced by 5-aminolevulinic acid (5-ALA) has been reported to detect more tumours compared with standard white-light (WL) cystoscopy. Most reports are from single centres with relatively few patients.

Objective: To evaluate whether 5-ALA-induced FL and WL cystoscopy at transurethral resection (TUR) is superior compared with standard procedures under WL only with respect to tumour recurrence and progression in patients with non–muscle-invasive bladder cancer.

Design, setting, and participants: This randomised, multicentre, observer- and pathologist-blinded, prospective phase 3 clinical trial enrolled 300 patients, and of those patients, 153 were randomised to FL cystoscopy and 147 were randomised to standard WL cystoscopy.

Intervention: All patients were first inspected under WL and all lesions were recorded. Patients randomised to FL underwent a second inspection. TUR was carried out in both groups.

Measurements: Control cystoscopy under WL was performed in all patients every 3 mo during the first year after randomisation and biannually thereafter.

Results and limitations: At the first TUR, the mean number of resection specimens per patient was 2.5 (FL: 2.5; WL: 2.4; $p = 0.37$) and the resulting mean number of resected tumours was 1.7 with FL and 1.8 with WL ($p = 0.85$). More patients were diagnosed with carcinoma in situ (CIS) in the WL group (13%) than in the FL group (4.2%). Within-patient comparison of FL patients only showed that FL detected more lesions than WL. Tumour lesions solely detected by FL cystoscopy that would not otherwise be detected by WL cystoscopy included 52% dysplasia, 33% CIS, 18% papillary neoplasms, 13% pT1, and 7% pTa. Outcome at 12 mo did not show any difference between groups with regard to recurrence-free and progression-free survival rates.

Conclusions: In this prospective, randomised, multi-institutional study, we found no clinical advantage of FL cystoscopy compared with WL cystoscopy and TUR.

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1. Introduction

Approximately 70% of all patients with newly diagnosed transitional cell bladder cancer have non-muscle-invasive bladder cancer (NMIBC) [1]. Initial treatment of such lesions consists of complete transurethral resection (TUR), but residual tumours are found in up to 78% of cases [2–8]. Furthermore, the probability of recurrence at 1 yr ranges from about 15% to 70% [9]. The high incidence of recurrence is mostly due to incomplete resection of the primary tumour and failure to resect nonvisible urothelial lesions.

A second resection 2–6 wk later is often performed in stage pT1 tumours to reduce the risk of incomplete resections but still does not result in destruction of nonvisible lesions [3]. White light (WL) is considered the reference standard for visualising tumours at cystoscopy, but its sensitivity and specificity is not entirely satisfactory [10,11].

In the past, numerous attempts have been made to develop optical markers for the detection of urothelial tumours to improve the clinical results of TUR. To date, 5-aminolevulinic acid (5-ALA)-induced fluorescent light (FL) cystoscopy has been studied most comprehensively, and long-term data are available [12–16].

The aim of the present study was to evaluate whether the addition of FL to WL cystoscopy would result in less recurrence and progression compared with WL only at TUR in patients with NMIBC. Only single-centre studies had been published when this study began.

2. Patients and methods

2.1. Inclusion criteria

Patients (>19 yr of age) with suspected NMIBC (first diagnosis or recurrence) based on at least one documented cystoscopy (Table 1) were included.

2.2. Exclusion criteria

Patients were excluded if they had a World Health Organisation general health status score of >2 (Eastern Cooperative Oncology Group), porphyria or hypersensitivity to porphyrins, renal and/or hepatic impairment, malignancies other than basalioma, pregnancy (planned or existing), or simultaneous participation in other trials.

2.3. Randomisation

Randomisation was performed first when the patient's written informed consent was obtained. The urologist telephoned the randomisation office and stated the person-number, age, gender, and risk group. These data made block randomisation possible, and the urologist was informed whether FL should be used or not.

2.4. Participating institutions

The study was conducted in the urology departments at Swedish university hospitals in Stockholm (Karolinska), Göteborg (Sahlgrenska), Lund, and Umeå and at the regional hospital in Örebro, Sweden. The urologists were specialists with particular interest in bladder cancer. For each patient, one urologist performed the TUR (and re-resection, if done) and another urologist performed the follow-up cystoscopies.

2.5. 5-Aminolevulinic acid instillation

Patients randomised to FL cystoscopy were given a single 1.5-g dose of 5-ALA hydrochloride (Medac GmbH, Wedel, Germany) dissolved in 50 ml of solvent and instilled into the urinary bladder prior to cystoscopy. The mean instillation time was 2.1 h (standard deviation [SD]: 0.7). All participating institutions had a D-light (Storz GmbH, Tuttlingen, Germany) providing blue light at 375–440 nm.

2.6. Cystoscopy and transurethral resection

In both groups, the bladder was first inspected under WL and the number and location of tumours and/or suspicious areas were noted. In the FL group, initial cystoscopy was performed under WL, followed by FL, and all suspected lesions were documented before TUR. All suspicious areas were biopsied, and TUR of identified papillary lesions was carried out in both groups. No immediate single instillation with mitomycin C was allowed after TUR.

2.7. Re-resection

All patients presenting with pT1G2–3 underwent a second resection 5–7 wk after initial TUR under WL. Both TURs were performed by the same surgeon. Random bladder biopsies were not allowed in either the first or the second TUR. Patients with pT2 tumours who were unfit for radical cystectomy were managed in the same way.

2.8. Follow-up

All patients were subjected to follow-up cystoscopy every 3 mo after the date of randomisation during the first year to detect suspicious areas within the bladder. All follow-up cystoscopies were carried out under WL until the end of the study (minimum of 12 mo after randomisation of the last study patient) or until tumour recurrence/first occurrence. During the second year, patients were followed with cystoscopy every 6 mo.

All follow-up treatments and cystoscopies were performed by another urologist who was not involved in the first and second TURs. To ensure the observer-blinded character of the study, the urologist did not know whether the first TUR had been performed with or without FL.

2.9. Bacillus Calmette-Guérin and mitomycin

Patients with confirmed carcinoma in situ (CIS), pTaG3, and pT1G2–3 tumours received the first bacillus Calmette-Guérin (BCG) instillation 4 wk after the last TUR. In case of contraindications to BCG or BCG side effects, intravesical mitomycin C was given. Regimens for BCG instillation were one instillation per week for 6 wk with or without maintenance therapy with one instillation per week for 3 wk at 3, 6, 12, 18, 24, and 30 mo.

2.10. Risk groups

All patients were divided into two prognostic risk groups. The high-risk group comprised patients with at least one of four risk factors (recurrent tumours, early recurrence \leq 12 mo, BCG within the last 12 mo, CIS). The low-risk group comprised patients without any of these risk factors.

2.11. End points

The study end point was reached either when a new tumour lesion had been detected within the follow-up period or when the patient had at least passed the 1-yr follow-up.

Table 1 – Demographic summary of patients with non–muscle-invasive bladder cancer, first cystoscopy results stratified by treatment, and first transurethral resection results according to reference pathology stratified by treatment (full-analysis set)^a

	White light	Fluorescent light	Overall
Patients, No.	138	141	279
Age, mean (SD), yr	68.9 (10.8)	70.1 (10.1)	69.5 (10.5)
Sex, n (%)			
Female	34 (24.6)	38 (27.0)	72 (25.8)
Male	104 (75.4)	103 (73.0)	207 (74.2)
History of NMIBC prior randomisation, n (%)			
No	69 (50.0)	67 (47.5)	136 (48.7)
Yes	69 (50.0%)	74 (52.5%)	143 (51.3%)
First cystoscopy, n (%)			
Exophytic tumour	119 (86.2)	124 (87.9)	243 (87.1)
Tumour base			
Flat lesion	11 (8.0)	14 (9.9)	25 (9.0)
Scar	30 (21.7)	54 (38.3)	84 (30.1)
TUR specimens evaluated per patient, mean (SD), n	1 (0.7)	6 (4.3)	7 (2.5)
Tumour specimens per patient, mean (SD), n	2.4 (1.7)	2.5 (1.8)	2.5 (1.7)
Staging/grading, n (%)	1.8 (1.5)	1.7 (1.5)	1.7 (1.5)
NA ^{**}	2 (1.4)	3 (2.1)	5 (1.8)
NE	0 (0.0)	3 (2.1)	3 (1.1)
No tumour	17 (12.3)	16 (11.3)	33 (11.8)
CIS	6 (4.3)	1 (0.7)	7 (2.5)
pTaG1–2	66 (47.8)	77 (54.6)	143 (51.3)
pTaG3, pT1G1–2	14 (10.1)	17 (12.0)	31 (11.2)
pT1G3	7 (5.1)	6 (4.3)	13 (4.7)
pT2	5 (3.6)	1 (0.7)	6 (2.2)
Dysplasia	9 (6.5)	6 (4.3)	15 (5.4)
PUNLMP	11 (8.0)	10 (7.1)	21 (7.5)
pTxG2	1 (0.7)	0 (0.0)	1 (0.4)
pTxG3	0 (0.0)	1 (0.7)	1 (0.4)
CIS, n (%)			
NA ^{**}	2 (1.4)	3 (2.1)	5 (1.8)
NE	0 (0.0)	3 (2.1)	3 (1.1)
No CIS	118 (85.5)	129 (91.5)	247 (88.5)
Isolated	6 (4.3)	1 (0.7)	7 (2.5)
Concomitant	12 (8.7)	5 (3.5)	17 (6.1)
Multifocal tumour, n (%)			
NA	2 (1.4)	3 (2.1)	5 (1.8)
NE	0 (0.0)	3 (2.1)	3 (1.1)
No tumour	17 (12.3)	16 (11.3)	33 (11.8)
No	58 (42.0)	53 (37.6)	111 (39.8)
Yes	61 (44.2)	66 (46.8)	127 (45.5)

CIS = carcinoma in situ; NA = not available; NE = not evaluable or missing; NMIBC = non–muscle-invasive bladder cancer; PUNLMP = papillary urothelial neoplasms of low malignant potential; SD = standard deviation; TUR = transurethral resection.
^a $p > 0.05$ (Wilcoxon-Mann-Whitney test); all parameters were homogeneously distributed between treatment arms.
^{**} Not histologically evaluated due to lack of suspicious tumour at cystoscopy.

2.12. Reference pathology

All specimens including suspected recurrences were first evaluated by the local pathologist who, as a rule, had a special interest in urologic pathology. The slides were subsequently sent to a reference pathologist (Gunilla Chebil, MD, Helsingborg, Sweden). All pathologists were unaware of whether or not FL was used.

2.13. Definitions

Cystoscopy was defined as a complete bladder inspection including urethra and prostate. Bladder tumours were classified morphologically according to the description by Mostofi [17]. Tumours were all lesions such as papillary tumours (Ta, T1–T4), CIS, and dysplasia, as determined by the reference pathologist. Progression was defined as worsening in T and G categories as well as newly diagnosed CIS. Recurrence rates at specific time points were measured based on the appropriate time-to-event analyses of the primary study end point. The number of patients with progressive disease during 1-yr follow-up was determined and analysed according to time-to-disease progression, defined as the date from randomisation to the first objective measurement of disease progression by the reference pathologist.

2.14. Sample size and power calculation

The sample size calculation was based on a assumed worst-rate scenario that the WL arm led to a 1-yr tumour rate of 30% based on previous studies [4,9]. Assuming that a clinical minimal superiority of 5-ALA-induced FL compared with WL of at least 15% was worth being detected, an FL-specific 1-yr tumour rate of 15% had to be specified. The probability of erroneously failing to reject the null hypothesis based on this working alternative hypothesis was limited to 20%, leading to a power of 80%. Assuming that all patients were followed for a minimum of 1 yr and that the hazard ratio was roughly constant over time, application of the nonparametric log-rank test led to a sample size of 135 per group, requiring that no dropouts occur within the follow-up period. Taking into consideration that roughly 15% of subjects entering the trial would drop out steadily within 12 mo after their entry, the sample size had to be increased to a minimum number of at least 142 patients per arm (nQuery Adviser v.3.0, Statistical Solutions Ltd, Cork, Ireland) within the full-analysis set. Assuming that roughly 5% of the enrolled patients would have to be excluded from the full analysis due to the decision for cystectomy after the first TUR, a total of 300 patients needed to be randomised into this clinical trial.

2.15. Ethical considerations

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines.

2.16. Statistical analysis

Statistical differences were calculated using the Wilcoxon rank sum or Mann-Whitney tests or log-rank tests. A *p* value of < 0.05 was considered statistically significant. The Kaplan-Meier technique was used to calculate the primary target criterion “time to tumour recurrence.” A two-sided confirmatory test was used at the significance level of 5% to compare the arm-specific Kaplan-Meier curves. The data analysis was performed using SAS v.8.02 (SAS, Cary, NC, USA) and StatXact (CYTEL Software Corp, Cambridge, MA, USA) software. The confirmatory proof of efficacy was performed within the full-analysis set, defined according to the intent-to-treat principle because all patients who were randomised into one treatment group actually underwent primary cystoscopy and were found to have no tumour, dysplasia, pTa, pT1, CIS, or pT2, except for those for whom a decision was made to perform cystectomy based on the result of the first TUR.

3. Results

Between 2002 and 2005, 300 patients with suspected NMIBC were randomised to either TUR with WL cystoscopy (*n* = 147) or TUR with WL plus FL cystoscopy (*n* = 153; Table 1). Of the 300 patients, 21 (7%) were excluded from the full-analysis set. Reasons for exclusion were radical cystectomy based on the results of the primary TUR (4.7%) and no first cystoscopy (2.3%). No differences were seen between the two treatment groups.

Four patients (1.4%) received adjuvant instillation therapy within 3 mo prior to study entry; two patients in each treatment group were treated either with BCG or mitomycin C.

3.1. Results at first cystoscopy

Among 279 patients, exophytic tumours were detected in 243 patients (87.1%), flat lesions were detected in 84 (30.1%), solid tumours were detected in 25 (9.0%), and scars were detected in 7 (2.5%) (Table 1). Flat lesions were documented more often in the FL group.

No tumour was diagnosed in 33 patients (11.8%) (WL: 12.3%; FL: 11.3%). No relevant differences between the treatment groups were observed with regard to staging and grading categories (Table 1). Isolated or concomitant CIS was diagnosed in 8.6% of patients (WL: 13.0%; FL: 4.2%). CIS lesions with different staging and grading categories were similar between the two treatment groups (Table 2).

3.2. Lesion detection rates of fluorescent and white light cystoscopy for within-patient comparison of fluorescent light-treated patients only

The analysis of within-patient comparison of FL versus WL cystoscopy showed that, generally, FL cystoscopy detected more lesions than WL cystoscopy. Tumour lesions solely

Table 2 – Frequency distribution of biopsy histology at first transurethral resection on a patient basis, focused on carcinoma in situ (CIS) lesions (full-analysis set)

	White light	Fluorescent light	Overall
Patients, No.	138	141	279
Any CIS, <i>n</i> (%)	18 (13.0)	6 (4.2)	24 (8.6)
CIS, <i>n</i> (%)	6 (4.3)	1 (0.7)	7 (2.5)
CIS, dysplasia, <i>n</i> (%)	2 (1.4)	–	2 (0.7)
CIS, pTaG2, <i>n</i> (%)	3 (2.2)	1 (0.7)	4 (1.4)
CIS, pTaG3, <i>n</i> (%)	1 (0.7)	2 (1.4)	3 (1.1)
CIS, pT1G2, <i>n</i> (%)	2 (1.4)	1 (0.7)	3 (1.1)
CIS, pT1G3, <i>n</i> (%)	3 (2.2)	1 (0.7)	4 (1.4)
CIS, pT2, <i>n</i> (%)	1 (0.7)	–	1 (0.4)

Table 3 – Tumour lesions solely detected by fluorescent-light-guided cystoscopy (full-analysis set)

	Overall, <i>n</i> (%)	Detected by fluorescent light only, <i>n</i> (%)
Carcinoma in situ	9 (100)	3 (33)
Dysplasia	21 (100)	11 (52)
Papillary neoplasm	22 (100)	4 (18)
pTa	150 (100)	10 (7)
pT1	23 (100)	3 (13)
pT2	1 (100)	–
pT3–4	1 (100)	–

detected by FL cystoscopy that would not otherwise be detected by WL cystoscopy included 52.4% of all dysplasias, 33.3% of all CIS, 18.2% of papillary neoplasms, 13% of pT1 tumours, and 6.7% of pTa tumours (Table 3).

3.3. Results of second cystoscopy

Second TUR in 25 high-risk patients was performed only under WL in both groups. Mean number of tumour specimens per patient was 1.1 (WL: 1.3; FL: 0.9; *p* = 0.331). The number of resected specimens evaluated per patient ranged between 1 and 7, and the mean number was higher in the FL group (2.4) than in the WL group (2.1) (*p* = 0.281).

3.4. Adjuvant intravesical instillation therapy

Patients with CIS, pTaG3, and pT1G2–3 tumours were candidates for BCG instillations. A total of 62 patients were eligible for instillation, of whom 44 (93.6%) received induction therapy with a mean of 5.6 instillations (SD: 1.5) per patient (WL: 24 patients; FL: 20 patients). Seven patients, six of them in the WL group, received maintenance therapy with a mean of 4.9 instillations (SD: 3.2) per patient.

3.5. Recurrence-free survival

Fig. 1 shows Kaplan-Meier estimates on recurrence-free survival. The analysis of all patients showed a recurrence-free survival rate at 12 mo of 55.9% (95% confidence interval, [CI], 46.8–64.0) in the WL group and of 55.1% (95% CI, 46.1–63.2) in the FL group (log-rank test, *p* = 0.689). The analysis

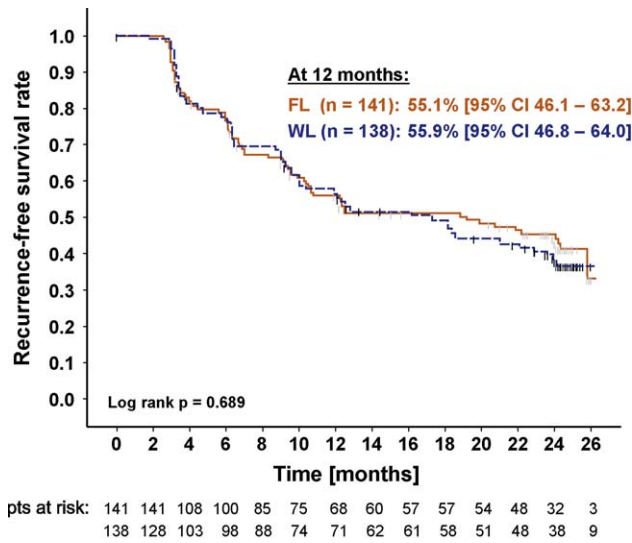


Fig. 1 – Recurrence-free survival at 12 months.

of patients with any histologically verified tumour at first TUR showed a recurrence-free survival rate at 12 mo of 53.1% (95% CI, 43.3–61.9) in the WL group and of 50.4% (95% CI, 40.9–59.2) in the FL group (log-rank test, $p = 0.979$).

Recurrence-free survival rates at 12 mo in the low-risk and high-risk groups of patients with any histologically verified tumour at first TUR are shown in Figs. 2 and 3, respectively.

3.6. Progression-free survival

At 12 mo, the analysis of all patients showed a progression-free survival rate of 89.1% (95% CI, 81.0–93.9) in the WL group and of 91.1% (95% CI, 82.8–95.5) in the FL group (Fig. 4). The difference between the two treatment groups did not reach statistical significance (log-rank test, $p = 0.109$).

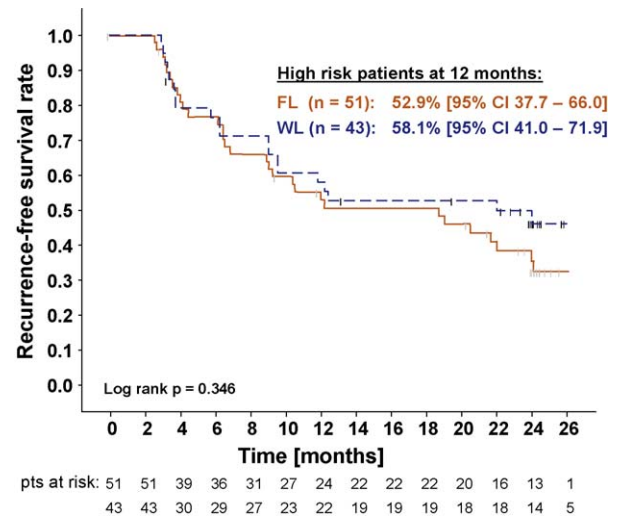


Fig. 3 – Recurrence-free survival for high-risk patients at 12 months.

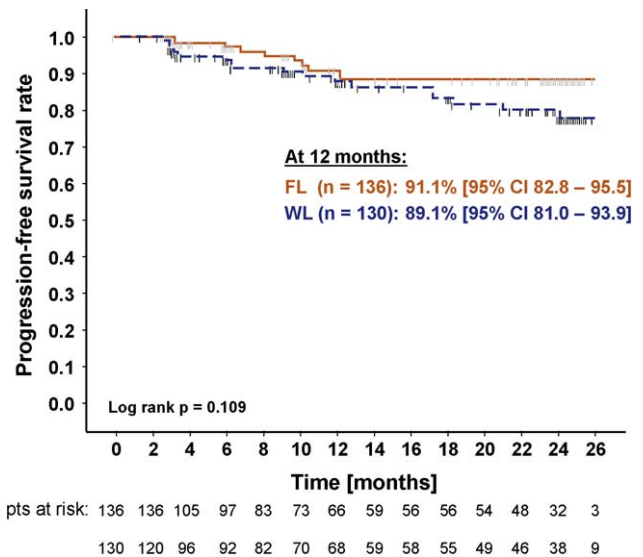


Fig. 4 – Progression-free survival at 12 months.

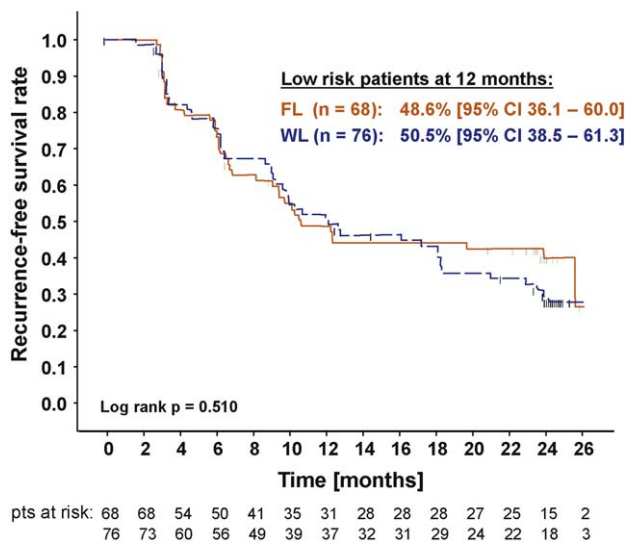


Fig. 2 – Recurrence-free survival for low-risk patients at 12 months.

3.7. Safety

Adverse events were reported in 22.9% of patients and occurred more often in the FL group (28%) than in the WL group (17.5%) without any instillation. Most adverse events observed were renal and genitourinary disorders (WL: 10.2%; FL: 13.3%).

Nine patients (WL: 4; FL: 5) died between 13 d and 735 d after first TUR. Causes of death in the WL group were cancer other than bladder ($n = 2$) and unknown ($n = 2$). In the FL group, reasons were progression of bladder tumour ($n = 1$), lung cancer ($n = 1$), pulmonary embolism ($n = 1$), bladder perforation ($n = 1$), and unknown ($n = 1$).

4. Discussion

This report is the first from a randomised, multicentre (five centres in Sweden), observer- and pathologist-blinded,

prospective phase 3 study that shows no benefit from using FL-guided cystoscopy in patients with NMIBC. The reasons for this surprising finding are not known.

One factor may be that our study included not only patients with newly diagnosed NMIBC but also patients with recurrent tumours. In the present study, half of the patients presented with recurrent bladder tumours prior to randomisation (Table 1). This factor contrasts with other studies in which mostly patients with newly diagnosed NMIBC were randomised to FL or WL [12,18]. Another reason might be a higher percentage of low-grade papillary tumours than in most published studies. The main advantage with FL is probably in visualising severe dysplasia and CIS, but only 21% of the patients in our study had high-grade tumours for which CIS, dysplasia, or both are common. Additionally, an imbalance for dysplasia and CIS existed between groups at first cystoscopy, although it was not statistically significant. Despite a median 5-ALA instillation time of 2.1 h (SD: 0.7), one may argue that instillation time was too short to carry out a high-quality cystoscopy under FL. One may then speculate as to whether the limited experience in FL TUR by the participating urologists in our study actually made a difference. Training with FL cystoscopy prior to the start of the study may have been simply insufficient. The authors from other patient series showing a superiority of FL compared with WL, as a rule, had much longer experience with FL [12,18–20].

Kriegmair et al first described 5-ALA-mediated fluorescence cystoscopy in 1992 [21]. A few years later, hexylaminolevulinat (HAL) was investigated with the goal of increasing the fluorescent intensity of photoactive porphyrins (PAP), decreasing the drug dose, and decreasing the instillation time, which is critical for patient compliance and higher tumour specificity [22]. HAL was selected over other n-alkyl-chain derivatives because of its satisfactory water solubility and capacity to induce high amounts of PAP at lower doses than 5-ALA. Marti et al, comparing 5-ALA with HAL for the detection of bladder tumours, found that HAL showed higher tumour selectivity, lower efficient concentration, shorter administration time needed, and deeper drug tissue penetration [23]. These factors may also explain why we did not find a benefit of FL-guided cystoscopy using 5-ALA in comparison with WL cystoscopy.

Recurrence and progression rate is reported as an end point when comparing FL-guided TUR with WL TUR; however, conflicting results with regard to recurrence rate have been reported. Three studies have shown that FL-guided TUR enhances recurrence-free survival rate at 24 mo compared with WL TUR [12,18,20]. In contrast, two studies presented at the 2007 congresses of the European Association of Urology and the American Urological Association did not find any difference in recurrence rate [24,25]. Alken et al reported the results from a multicentre trial that included 36 centres from Germany investigating the effect of 5-ALA-induced FL cystoscopy and TUR versus WL cystoscopy and TUR [24]. In that study, 1048 patients were initially randomised. The authors found no difference between groups in the rate of residual tumour at second resection 4

wk after first TUR (FL: 29% vs WL: 29.2%). In addition, recurrence-free survival at 24 mo was similar between groups (FL: 82% vs WL:81%; log-rank test, $p = 0.93$) [24]. Similarly, Penkoff et al reported the results of a randomised, double-blind, placebo-controlled, multicentre, prospective phase 3 clinical trial in which 5-ALA-induced FL was compared with WL cystoscopy [25]. In that study, 381 patients were randomised. No significant difference was found when comparing 140 patients who underwent FL evaluation and 150 patients who underwent WL cystoscopy with regard to 12-mo recurrence-free survival (FL: 62%; WL: 70%) [25]. Furthermore, recurrence-free survival was independent of risk group. The authors appropriately noted that FL improved the detection rate of tumour lesions, but this visual improvement did not appear to translate into improved recurrence-free survival rates [25]. Some studies have shown that CIS and/or dysplasia are more easily detected using FL [10,13,14,16,26,27]. This finding is important but does not necessarily change therapeutic management because patients with TaG3 or T1 tumours should be treated with BCG, regardless of whether a small area of CIS is found. If CIS is diagnosed at the first cystoscopy control after BCG treatment, a cystectomy is strongly advised, regardless of whether CIS was diagnosed before BCG.

A considerable number of articles have been published that all show superiority of FL over WL. Most studies, however, are from single institutions, are limited in the number of patients, and have short follow-up. Consequently, it is imperative that the clinical benefit using 5-ALA FL cystoscopy be substantial and firmly proven. The studies published so far have emphasised the positive sides of FL, but the excellent results published by enthusiasts cannot be transferred directly to all urology units. Large clinical studies are extremely important.

5. Conclusions

FL cystoscopy with 5-ALA did not detect more NMIBC tumours than WL cystoscopy. Comparing the 12-mo outcome, there were no differences between treatment groups with regard to recurrence-free survival or progression-free survival rates. In comparison with the group of patients receiving no treatment, the instillation of 5-ALA was safe and well tolerated.

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Study concept and design: Wiklund.

Acquisition of data: Wiklund, Holmäng, Davidsson, Friedrich, Pedersen.

Analysis and interpretation of data: Schumacher, Holmäng, Wiklund.

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References

- [1] Holmang S, Hedelin H, Anderstrom C, Holmberg E, Johansson SL. Prospective registration of all patients in a geographical region with newly diagnosed bladder carcinomas during a two-year period. *Scand J Urol Nephrol* 2000;34:95–101.
- [2] Vogeli TA, Grimm MO, Simon X, Ackermann R. Prospective study of effectiveness. Reoperation (re-TUR) in superficial bladder carcinoma [in German]. *Urologe A* 2002;41:470–4.
- [3] Schips L, Augustin H, Zigeuner RE, et al. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? *Urology* 2002;59:220–3.
- [4] Schwaibold HE, Sivalingam S, May F, Hartung R. The value of a second transurethral resection for T1 bladder cancer. *BJU Int* 2006;97:1199–201.
- [5] Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. *J Urol* 1999;162:74–6.
- [6] Klän R. Residual tumor discovered in routine second transurethral resection in patients with stage T1 transitional cell carcinoma of the bladder. *J Urol* 1991;146:316–8.
- [7] Zurkirchen MA, Sulser T, Gaspert A, Hauri D. Second transurethral resection of superficial transitional cell carcinoma of the bladder: a must even for experienced urologists. *Urol Int* 2004;72:99–102.
- [8] Köhrmann K. Der Wert der transurethralen Nachresektion beim oberflächlichen Harnblasenkarzinom. *Akt Urol* 1994;25:208–13.
- [9] Sylvester RJ, van der Meijden APM, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49:466–77, discussion 475–7.
- [10] Jocham D, Witjes F, Wagner S, et al. Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: a prospective, phase III multicenter study. *J Urol* 2005;174:862–6, discussion 866.
- [11] Jakse G, Algaba F, Malmström P-U, Oosterlinck W. A second-look TUR in T1 transitional cell carcinoma: why? *Eur Urol* 2004;45:539–46, discussion 546.
- [12] Denzinger S, Burger M, Walter B, et al. Clinically relevant reduction in risk of recurrence of superficial bladder cancer using 5-aminolevulinic acid-induced fluorescence diagnosis: 8-year results of prospective randomized study. *Urology* 2007;69:675–9.
- [13] Filbeck T, Pichlmeier U, Knuechel R, Wieland WF, Roessler W. Clinically relevant improvement of recurrence-free survival with 5-aminolevulinic acid induced fluorescence diagnosis in patients with superficial bladder tumors. *J Urol* 2002;168:67–71.
- [14] Fradet Y, Grossman HB, Gomella L, et al. A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. *J Urol* 2007;178:68–73, discussion 73.
- [15] Grossman HB, Gomella L, Fradet Y, et al. A phase III, multicenter comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of superficial papillary lesions in patients with bladder cancer. *J Urol* 2007;178:62–7.
- [16] Jichlinski P, Guillou L, Karlsen SJ, et al. Hexyl aminolevulinate fluorescence cystoscopy: new diagnostic tool for photodiagnosis of superficial bladder cancer—a multicenter study. *J Urol* 2003;170:226–9.
- [17] Mostofi F. *Histological typing of urinary bladder tumors*. International classification of tumors, 19. Geneva, Switzerland: World Health Organisation; 1973.
- [18] Danilchenko DI, Riedl CR, Sachs MD, et al. Long-term benefit of 5-aminolevulinic acid fluorescence assisted transurethral resection of superficial bladder cancer: 5-year results of a prospective randomized study. *J Urol* 2005;174:2129–33, discussion 2133.
- [19] Kriegmair M, Zaak D, Rothenberger KH, et al. Transurethral resection for bladder cancer using 5-aminolevulinic acid induced fluorescence endoscopy versus white light endoscopy. *J Urol* 2002;168:475–8.
- [20] Babjuk M, Soukup V, Petrik R, Jirsa M, Dvoracek J. 5-aminolevulinic acid-induced fluorescence cystoscopy during transurethral resection reduces the risk of recurrence in stage Ta/T1 bladder cancer. *BJU Int* 2005;96:798–802.
- [21] Kriegmair M, Baumgartner R, Hofstetter A. Intravesikale Instillation von Delta-Aminolävulinsäure (ALA)—eine neue Methode zur photodynamischen Diagnostik und Therapie. *Laser Med* 1992;8:83.
- [22] Fotinos N, Campo MA, Popowycz F, Gurny R, Lange N. 5-Aminolevulinic acid derivatives in photomedicine: characteristics, application and perspectives. *Photochem Photobiol* 2006;82:994–1015.
- [23] Marti A, Jichlinski P, Lange N, et al. Comparison of aminolevulinic acid and hexylester aminolevulinate induced protoporphyrin IX distribution in human bladder cancer. *J Urol* 2003;170:428–32.
- [24] Alken P, Siegmund M, Gromoll-Bergmann K, Daffner P, Fenner W, Spelz J. A randomized controlled multicentre trial to compare the effects of transurethral resection of bladder carcinomas under 5-ALA induced fluorescence light to conventional white light. In: *Proceedings from the Annual Congress of the European Association of Urology*; March 21–24, 2007; Berlin, Germany. Abstract 593.
- [25] Penkoff H, Steiner H, Dajc-Sommerer E. Transurethral detection and resection of bladder carcinomas under white or 5-ALA induced fluorescence light: results of the first double-blind-placebo controlled clinical trial [abstract 1085]. *J Urol* 2007;177(Suppl):358.
- [26] Schmidbauer J, Witjes F, Schmeller N, Donat R, Susani M, Marberger M. Improved detection of urothelial carcinoma in situ with hexaminolevulinate fluorescence cystoscopy. *J Urol* 2004;171:135–8.
- [27] Zaak D, Frimberger D, Stepp H, et al. Quantification of 5-aminolevulinic acid induced fluorescence improves the specificity of bladder cancer detection. *J Urol* 2001;166:1665–8, discussion 1668–9.