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Published in:
Scandinavian Journal of Urology

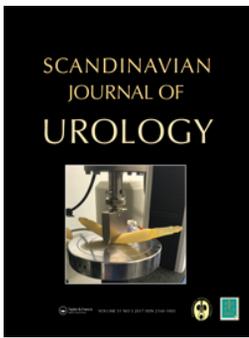
DOI:
[10.1080/21681805.2017.1353542](https://doi.org/10.1080/21681805.2017.1353542)

Publication date:
2017

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):
Mogensen, K., Glenthøj, A., Toft, B. G., Scheike, T., & Hermann, G. G. (2017). Outpatient photodynamic-guided diagnosis of carcinoma in situ with flexible cystoscopy: an alternative to conventional inpatient photodynamic-guided bladder biopsies in the operating theatre? *Scandinavian Journal of Urology*, 51(5), 376-380.
<https://doi.org/10.1080/21681805.2017.1353542>



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To cite this article: Karin Mogensen, Anders Glenthøj, Birgitte Grønkær Toft, Thomas Scheike & Gregers Gautier Hermann (2017) Outpatient photodynamic-guided diagnosis of carcinoma in situ with flexible cystoscopy: an alternative to conventional inpatient photodynamic-guided bladder biopsies in the operating theatre?, *Scandinavian Journal of Urology*, 51:5, 376-380, DOI: [10.1080/21681805.2017.1353542](https://doi.org/10.1080/21681805.2017.1353542)

To link to this article: <https://doi.org/10.1080/21681805.2017.1353542>



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Published online: 26 Jul 2017.



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Outpatient photodynamic-guided diagnosis of carcinoma *in situ* with flexible cystoscopy: an alternative to conventional inpatient photodynamic-guided bladder biopsies in the operating theatre?

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ABSTRACT

Objective: The aim of this prospective open comparative study was to establish whether conventional photodynamic-guided bladder biopsies using general anaesthesia and rigid resectoscopes (inpatient) can be replaced with less traumatic flexible cystoscopy in non-sedated patients (outpatient), without compromising the diagnosis of carcinoma *in situ* (CIS).

Materials and methods: Thirty-one patients were included. After BCG instillation for CIS, bladder biopsies were obtained using photodynamic-guided flexible cystoscopy. Two weeks later, patients underwent the conventional inpatient procedure. An external pathologist reviewed the biopsy samples. Pain and quality of life (QoL) symptom score were recorded.

Results: Post-BCG biopsies showed only CIS in 10 patients; high-grade Ta or T1 tumour in three patients, who were referred for cystectomy; and normal or low-grade tumour tissue in 18 patients. There was a high agreement of identification of high-grade disease in biopsies and cytology using the two methods ($\kappa = 0.93$, 95% confidence interval 0.8–1.0). The outpatient procedure identified four high-grade patients diagnosed as ‘normal/low-grade’ in the inpatient procedure. The opposite was observed in two patients. Quality of biopsies did not differ between the two procedures. Pain scores for outpatients were low, and median QoL symptom score was significantly lower than for inpatients (24 vs 33, $p = 0.02$). Hospital length of stay was significantly longer for inpatients.

Conclusions: Outpatient photodynamic-guided flexible cystoscopy is less traumatic than the conventional inpatient procedure in the diagnosis of CIS. It is safe and cost-effective, and may be an alternative to conventional inpatient biopsy procedures in patients with malignant urine cytology and normal white-light cystoscopy.

ARTICLE HISTORY

Received 23 March 2017
Revised 9 June 2017
Accepted 2 July 2017

KEYWORDS

Biopsy; CIS; outpatient; photodynamic diagnosis

Introduction

Carcinoma *in situ* (CIS) of the bladder is a flat, high-grade non-invasive urothelial cancer, which, if left untreated, has a high mortality rate [1,2]. Immunotherapy with instillation of BCG is the recommended treatment [3]. European Association of Urology (EAU) [4] and American Urological Association (AUA) [5] guidelines stress the risk of disease progression in CIS, and the importance of biopsies to ensure a correct diagnosis [5,6].

In accordance with both guidelines, fluorescence-guided cystoscopy using photodynamic diagnosis (PDD, blue-light cystoscopy) detects significantly more CIS lesions in the bladder than cystoscopy without fluorescence [7,8]. Therefore, photodynamic-guided cystoscopy is recommended for diagnosis of CIS [4,5].

PDD is performed in an inpatient setting in the operating theatre (OT), under general anaesthesia and with rigid 26 Fr resectoscopes. New flexible 16 Fr cystoscopes for fluorescence cystoscopy have recently been made available for outpatient

use where sedation is not required [9]. Biopsy techniques have been developed for flexible cystoscopes that will provide biopsies of sufficient quality for diagnosis of bladder tumour stages as advanced as stage T1b and are routinely performed in our outpatient department (OPD) [10]. Techniques are now available for carrying out fluorescence-guided biopsies of the bladder in the OPD with substantially less impact on the patient than in the conventional inpatient procedure.

CIS mostly affects elderly patients, who are generally less fit for surgery and general anaesthesia [11]. A less aggressive outpatient diagnostic procedure for CIS as outlined in this study may reduce patient morbidity and consume fewer healthcare resources.

The aim of this study was to establish whether outpatient photodynamic-guided flexible cystoscopy in awake non-sedated outpatients could be an alternative to photodynamic-guided biopsies taken in the OT using rigid cystoscopy in anaesthetized patients without significantly compromising the diagnosis of CIS, and whether this would

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be more acceptable to patients, while placing fewer demands on the healthcare system.

Materials and methods

The study was a prospective open comparative study, with the patients as their own control.

Approval was obtained from the Danish Ethical Committee (H-4-2011-123) and the Danish Data Protection Agency (2014-41-3109). The study was registered in ISRCTN (ISRCTN48222814).

Patients

Patients were included if they had histologically confirmed primary or secondary CIS and had completed a course of six weekly BCG treatments. The main exclusion criteria were porphyria, macroscopic haematuria, fewer than six BCG treatments, urinary tract infection and allergy to hexaminolevulinic hydrochloride (Hexvix[®]; Photocure ASA, Oslo, Norway). Previous radiotherapy of the bladder was not an exclusion criterion.

From December 2012 to March 2016, 62 consecutive patients commenced BCG treatments. Fifteen patients did not fulfil the inclusion criteria and 16 patients did not want to participate (two preferred general anaesthesia and 14 could not commit to regular hospital visits). Thirty-one patients were included in the study. The median age was 72 years (range 48–89 years). The indication for BCG was only CIS in 21 patients and concurrent CIS in 10 patients (CIS + Ta high grade: nine patients; CIS + T1a high grade: one patient). All 31 patients completed the study.

Written informed consent was obtained from all patients.

Outpatient procedure

Voided urine was collected in all patients before instilling hexaminolevulinic, and sent for cytological analysis. One hour before cystoscopy, 50 ml hexaminolevulinic and 20 ml lidocaine were instilled into the bladder; all patients took 1 g paracetamol and all but one patient took 600 mg ibuprofen.

The patient was asked to empty the bladder after 1 h to remove urine and thereby reduce green autofluorescence from the urine during the PDD procedure.

Cystoscopy was performed in white and blue light using a flexible 16 Fr PDD video cystoscope with a suction channel (PDD 11272 VPI, D-Light C Light source; Karl Storz, Tuttlingen, Germany). All suspicious lesions were recorded on a bladder map and biopsies were taken with flexible biopsy forceps (single-action jaws, 5 Fr, length 73 cm). No cauterization of the biopsy areas was carried out.

Immediately after the OPD procedure, patients recorded pain on a visual analogue scale (VAS) ranging from 0 to 10, with 0 being no pain.

All data were blinded until after the following inpatient procedure.

Inpatient procedure

Two weeks later, patients were hospitalized to undergo the photodynamic-guided procedure repeated under general

anaesthesia. A xenon light source (D-light C system[®]) fitted with a light filter and a three-chip pendulum camera on a 26 Fr resectoscope, and a short-jaw biopsy forceps (Karl Storz, Germany) were used in the OT. The OPD procedure 2 weeks earlier did not influence the inpatient procedure as mucosal lesions from the biopsies had healed and could not be identified. Two skilled urologists performed all of the procedures. No patient had the two cystoscopies carried out by the same urologist.

All biopsies and urine samples were consecutively examined by the local pathologist, and after study completion they were also examined by an external pathologist using the WHO 2004 histological classification of urothelial carcinoma [12]. Urinary cytology was ranked as: 'normal cells', 'atypical cells' or 'malignant cells'.

Quality of life assessment

The Quality of Life Questionnaire for Non-Muscle-Invasive Bladder Cancer (QLQ NMIBC24; EORTC, Brussels, Belgium) was completed by the patients after each procedure. This questionnaire has been validated in a study measuring quality of life (QoL) after transurethral resection of bladder tumours in the OT [13]. In that study, a score based on five symptoms was calculated to assess lower urinary tract symptoms (LUTS) due to endoscopy.

Statistical analysis

The one-sample *t* test and Wilcoxon signed rank test were used to test differences in patients' symptoms caused by the cystoscopy and biopsy procedure in the two settings. These tests were conducted using the paired structure, where each subject is his or her own control. The differences were approximately normally distributed when conducting *t* tests. For the comparison of the 2 by 2 diagnostic tables, McNemar's chi-squared test was used to test differences in the ability of the OT and OPD procedures to diagnose CIS. This adjusts for the fact that there was a paired comparison. To describe the extent to which the OT and the OPD procedures give the same diagnosis, the Cohen kappa coefficient (κ) was calculated. The statistical computing program R version 3.2.0 was used for all statistical analyses, with the psych package for computation of the Cohen κ .

Results

Histology and cytology

There was no significant difference between the procedures regarding their ability to identify high-grade disease in biopsies ($p=0.68$) (Table 1), and the concordance in the histological diagnosis between the two procedures showed a Cohen κ of 0.56 [95% confidence interval (CI) 0.25–0.86]. The OPD procedure identified four high-grade patients who were diagnosed as 'normal' or low-grade disease in the OT. The opposite was observed in two patients (Table 1).

Table 1. Diagnosis of high-grade Ta/T1 or carcinoma *in situ* (CIS) lesions versus low-grade or normal findings based on histological examination of biopsies from the outpatient department and operating theatre after BCG treatment (results of urine cytology not included).

Outpatient department	Operating theatre		
	Normal/low grade (n)	High grade, CIS (n)	Total
Normal/low grade (n)	18	2	20
High grade, CIS (n)	4	7	11 (11/13, 85%)
Total	22	9 (9/13, 69%)	31

Table 2. Diagnosis of high-grade Ta/T1 or carcinoma *in situ* (CIS) lesions versus low-grade lesions or normal findings based on histological examination of biopsies and of urine cytology from the outpatient department and operating theatre after BCG treatment.

Outpatient department	Operating theatre		
	Normal/low grade (n)	High grade, CIS (n)	Total
Normal/low grade (n)	18	1	19
High grade, CIS (n)	0	12	12 (12/13, 92%)
Total	18	13 (13/13, 100%)	31

Table 3. Characteristics of biopsies obtained through flexible cystoscopy in the outpatient department (OPD) and through rigid endoscopes in the operating theatre (OT).

	OPD	OT
No. of biopsies per patient, mean (range)	3.9 (2–6)	4.5 (3–7)
Maximal size (mm)	2 × 2 × 2	7 × 2 × 2
Depth of biopsy		
Lamina propria, superficial part	22 (18.5)	23 (17)
Lamina propria, deep part	76 (63)	88 (63)
Detrusor muscle	22 (18.5)	28 (20)
Total	120 (100)	139 (100)
Quality of biopsies for histopathological evaluation		
Suitable for diagnosis	109 (90)	136 (97)
Less suitable for diagnosis	11 (9)	3 (2)
Not suitable for diagnosis	1 (1) ^a	2 (1) ^a
Total	121	141

Data are shown as n (%) unless otherwise indicated.

^aNo urothelium, ulcer.

In all but one patient with high-grade/CIS, malignant cells were found in voided urine. No patients with low-grade disease had malignant cells in their urine. If these malignant cells in the urine are considered to be diagnostic for high-grade disease, even in patients where the biopsy indicates low-grade disease or no disease, the agreement between the diagnoses from OPD and OT becomes very high, giving similar results ($p = 1.0$; $\kappa = 0.93$; 95% CI 0.8–1.0) (Table 2).

The number of biopsies taken, and the depth and quality of biopsy for histopathological evaluation did not differ between the two procedures (Table 3).

In 10 patients, histology showed only CIS; these patients underwent a repeat BCG course. Three patients progressed by developing exophytic high-grade Ta or T1 tumour, one with concurrent CIS, and were referred for evaluation for radical cystectomy. Eighteen patients had normal biopsies or low-grade tumour and entered maintenance BCG treatment.

Pain scores and QoL assessment

The median VAS score for pain experienced during the OPD procedure was 1.5 (range 1–4).

All 31 QLQ-NMIBC24 questionnaires were returned after the OPD procedure, and 29 after the OT procedure. The LUTS score was significantly lower after the OPD procedure

(median 24, range 0–80) than after the OT procedure (median 33, range 5–72, $p = 0.02$).

Length of procedure

Hospital length of stay was significantly longer for the OT procedure. Median OT surgery time was 67 min (range 39–96 min); the surgery itself took a median of 20 min (range 9–46 min). Including the presurgery day, 21 patients were discharged on the second day of hospitalization; eight were discharged on day 3 and two on day 4. One patient was readmitted because of urine retention after the procedure in the OT with the rigid cystoscope. He stayed one night at the hospital and was discharged with an indwelling urinary catheter, which he retained for 8 days.

By contrast, the OPD procedure took a median of 17 min (range 10–26 min). The entire procedure from arrival until discharge lasted for about 2 h: 1 h for hexaminolevulinate instillation and retention time and 1 h for the procedure, dressing and so on. One patient had haematuria requiring an indwelling catheter and bladder irrigation, with an additional one-night stay.

Discussion

This study demonstrated that photodynamic-guided cystoscopy using flexible cystoscopes may be an alternative to conventional photodynamic-guided cystoscopy carried out in the OT with general anaesthesia in the diagnosis of CIS. Photodynamic-guided biopsy in the OPD is safe, well tolerated and associated with significantly fewer postprocedural symptoms, compared to the procedure and biopsies obtained in the OT.

Urinary cytology had a higher sensitivity for the diagnosis of malignancy than did biopsy. The guidelines from the EAU recommend that photodynamic-guided biopsies should be considered following BCG treatment of CIS [4]. This study suggests that biopsy may not be needed if urinary cytology is negative. Urinary cytology could thus be used for primary surveillance together with white-light cystoscopy using flexible cystoscopes. If cytology contains cells that are suspicious

for malignancy, photodynamic-guided biopsies can be carried out with flexible cystoscopes in the OPD. Admission for inpatient inspection may be avoided, along with stressful procedures for the patients, while sparing health system resources.

Van Rhijm et al. [14] reported similar sensitivity and specificity of cytology for high-grade and CIS lesions in an inpatient setting. Haase and Harving [15] and Swietek et al. [16] also found a close correlation between positive cytology and CIS, and concluded that office-based white-light cystoscopy with urinary cytology may be sufficient follow-up after BCG, while biopsies should be taken only if the results are positive. One study even suggests that urine cytology alone may be sufficient follow-up in patients with CIS at risk of late progression after 10 years of follow-up [17].

Urinary cytology should not be used as the sole method for evaluation of treatment. In cases of malignant cells in urine, biopsies are essential to determine possible disease progression which may require more radical treatment [5].

In both procedures, all biopsies contained lamina propria, allowing a diagnosis of invasive disease. If invasive disease is diagnosed the patient should undergo resection of the biopsy area in the OT.

EAU guidelines recommend that photodynamic-guided biopsies following BCG treatment should be carried out 3–6 months after treatment. In Denmark, patients have photodynamic-guided biopsies after 6 weeks to assess early treatment response and to allow for rapid decisions on subsequent treatment; in the present study, three patients were referred for cystectomy. It has been claimed that photodynamic-guided cystoscopy within 3 months of BCG instillation is difficult owing to false-positive fluorescence and inflamed tissue confounding the visualization of CIS [18,19]. In an attempt to standardize false-positive fluorescence, only patients who had had a full course of six weekly treatments of BCG were included in the study. The pathologists did not observe significant tissue inflammation and false-positive fluorescence was not a problem during cystoscopy. The number of cases where there were insufficient biopsies for histopathological diagnosis was low and similar in the two settings.

False-positive fluorescence was observed and evaluated by Ray et al. in their inpatient study on photodynamic-guided biopsies following BCG instillations [20]. Although false-positive rates were relatively high for both blue (63%) and white (72%) light, the authors concluded that blue-light cystoscopy was still valuable if urine cytology was positive. Evaluation of the specificity and sensitivity of the individual photodynamic-guided bladder biopsy has been reported previously and was therefore not the topic of this project [21,22]. The outpatient procedure is challenged by patient compliance, biopsy technique, confounding autofluorescence from urine during PDD [23] and the limited possibility of removing blood and urine by bladder irrigation through the small, flexible cystoscopes during the procedure. This entire procedure has not previously been evaluated and reported.

The limitation of this study is that biopsies were taken about 3 months earlier than recommended by the EAU [4], which may limit comparison of the results with other studies.

However, early biopsies resulted in an earlier diagnosis and subsequent referral for radical cystectomy of three study patients with high-grade tumour at the time of biopsy, which may have a beneficial influence on the course of the disease.

The endoscopy time used for the PDD cystoscopy procedure, including biopsies, was the same in both settings. Owing to the requirement for general anaesthesia in the OT, patient stay was longer, and one-third of patients stayed overnight. The OPD procedure where the patients went home immediately after the biopsy procedure was significantly more convenient for patients. Staff requirements were also considerably lower. Treatment in the OT requires an anaesthetist, a nurse anaesthetist, a urologist, a scrub nurse and an assistant on the floor, as well as urology ward staff, while the OPD requires only a nurse and a doctor. The office-based procedure is therefore highly cost-effective and not associated with an increase in adverse events. With a pain VAS score of 1.5 and a 27% reduction in symptom score, the well-being of the OPD patient is not at risk.

In conclusion, photodynamic-guided diagnosis using flexible cystoscopy may be an alternative in the diagnosis of CIS to conventional inpatient photodynamic-guided cystoscopy in sedated patients following a full course of BCG therapy. The outpatient procedure which uses flexible cystoscopy is safe and well tolerated, has less impact on patient QoL and is cost-effective compared to inpatient procedures. In addition, this study supports the practice that voided urinary cytology is valuable as a monitoring tool for CIS.

Acknowledgement

We are grateful to the EORTC Quality of Life Group, Brussels, for permission to use their quality of life questionnaire QLQ-NMIBC24.

Disclosure statement

Gregers G. Hermann has provided services as a speaker in meetings funded by Photocure. None of the other authors has any disclosures to make.

Funding

Fondation Juchum and Photocure AS provided financial support for the study.

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