The Quality of 5-Aminolevulinic Acid-Induced Photodynamic Diagnosis and Transurethral Resection of Bladder Tumors: Does the Urologist Play a Role?

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Key Words

Bladder cancer • Photodynamic diagnosis • Aminolevulinic acid • Transurethral resection • Recurrence

Abstract

Introduction: The aim of this study is to evaluate the quality of photodynamic diagnosis (PDD) and transurethral resection of bladder tumors (TURBT) among different urologists.

Patients and Methods: The selected data consists of 194 patients, 268 5-aminolevulinic acid (5-ALA)-induced PDD procedures and 934 biopsies. Tumors were resected and biopsies were taken from suspicious areas under guidance of white light endoscopy and 5-ALA-induced fluorescence cystoscopy. The quality of PDD was determined by evaluating the mean number of tumors resected by 5 urologists and, thereafter, assessing the time to recurrence between groups.

Results: Urologist 1 took 37% more biopsies ($p < 0.001$) and diagnosed 42% more tumors ($p = 0.005$) and 46% more false positives ($p < 0.001$) from bladders compared to urologists 2, 3, 4 and 5 together. The mean time to bladder cancer recurrence for all recurrences within 0–18 months was 11.0 months for operator 1 and 8.3 months for the other urolo-

gists ($p = 0.01$). **Conclusions:** The resecting urologist appears to be an important factor for the quality of standard and PDD-assisted TURBT. Learning curve programs may be required with experienced surgeons accompanying those with less experience.

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Introduction

Transurethral resection of bladder tumors (TURBT) remains the gold standard for the initial diagnosis and treatment of bladder cancer. Photodynamic diagnosis (PDD) or fluorescence cystoscopy is a technique which uses blue light to enhance the detection of occult bladder tumors, especially carcinoma in situ which is a flat malignant lesion associated with a relatively poor prognosis [1]. The overall sensitivity of fluorescence cystoscopy is 95%, versus 70% for white light endoscopy (WLE) [2].

Fluorescence cystoscopy is achieved by instilling the bladder with 5-aminolevulinic acid (5-ALA) or its hexyl ester derivative (hexaminolevulinic acid or HAL)

Table 1. Patient characteristics (n = 434)

	Surgeon 1 n (%)	Surgeons 2, 3, 4 and 5 n (%)	p value ¹	Other surgeons	p value ¹
Procedures	119	149		166	
Age (mean)	68.3	66.1	0.10	65.6	0.03*
Gender ²					
Women	31 (26)	32 (21)		44 (27)	
Men	88 (74)	117 (79)	0.38	122 (73)	0.93
Prior recurrence rate					
Primary patients	64 (54)	72 (48)	0.38	108 (65)	0.06
≤1 recurrence per year	29 (23)	42 (28)	0.31	28 (17)	0.22
>1 recurrence per year	28 (23)	35 (24)	0.99	30 (18)	0.26
Category					
Ta	44 (51)	74 (73)	0.02*	70 (66)	0.04*
T1	19 (22)	18 (18)	0.47	23 (22)	0.95
T2	16 (19)	6 (6)	0.007*	10 (9)	0.07
T3	0 (0)	0 (0)	N/A	0 (0)	N/A
CIS only	7 (8)	3 (3)	0.12	3 (3)	0.10
CIS present					
No	75 (87)	94 (93)		97 (92)	
Yes	11 (13)	7 (7)	0.18	9 (8)	0.34
Grade ³					
G1	26 (33)	37 (38)	0.51	32 (32)	0.85
G2	33 (42)	42 (43)	0.90	47 (47)	0.54
G3	19 (25)	18 (19)	0.35	21 (21)	0.60
Re-TURBT ⁴					
<6 weeks after PDD	0 (0)	3 (3)	0.12	1 (1)	0.36
<12 weeks after PDD	8 (11)	8 (9)	0.60	8 (10)	0.72

* p < 0.05. CIS = Carcinoma in situ; N/A = not applicable.

¹ Surgeon 1 is the reference. ² Exceeds the total number of procedures due to double counts. ³ Five procedures with unknown grading. ⁴ Repeat TURBT calculated from 552 procedures without data exclusion.

which has a better bioavailability. It is assumed that the recurrence rates are equal for 5-ALA and HAL [3] and that data for 5-ALA and HAL are generally transferable [4].

The major disadvantage of PDD is the relatively low specificity. The false-positive rate of 5-ALA-induced PDD is approximately 38% [5]. False fluorescence is associated with inflammation as a result of previous intravesical chemotherapy and recent TURBT, female gender [6, 7] and tangential illumination of the bladder wall with blue light [8]. The urologist might be an important factor for PDD specificity and the overall quality of PDD.

The aim of this study was to investigate the quality of 5-ALA-induced PDD among urologists, i.e. to evaluate the mean number of tumors resected from bladders and assessing the time to recurrence between groups.

Patients and Methods

Patients

Procedures were performed between November 1998 and January 2008 at our multidisciplinary bladder clinic. Patients eligible for PDD are all patients with symptoms of bladder cancer who are scheduled for a TURBT. Data from 306 patients, 552 procedures and 1,874 biopsies were collected and prospectively entered into a database (table 1). Patients with TURBT or intravesical therapy up to 90 days before the fluorescence cystoscopy were excluded from the analyses, because these factors are known to cause false fluorescence [7]. Exclusion resulted in a selected data set of 280 patients and 434 procedures (fig. 1). The 434 PDD-assisted TURBTs were performed by 13 different surgeons. Five surgeons carried out 268 procedures (62%). The remaining 8 urologists performed only a mean of 13 procedures per operator which was considered to be too low to calculate reliable recurrence rates and, therefore, the data from these 8 urologists were not used for analysis. All the surgeons started to use fluorescence cystoscopy during this period at our facility. Surgeons 1, 2 and 3 performed more than 500 TURBTs before commencing their first PDD.

Fig. 1. Flowchart of the data used for analysis. IVT = Intravesical therapy. ^aIncluding doubles (patients were treated multiple times by different urologists).

All patients were treated according to Dutch Urological Association and European Association of Urology guidelines. A repeat transurethral resection within 2–6 weeks was indicated after incomplete resection when biopsy specimens did not contain muscle tissue or when a non-muscle invasive high-grade tumor was found. Repeat TURBTs could not always take place exactly after 6 weeks due to operating waiting lists and were therefore performed within 6–10 weeks after the initial TURBT. All patients underwent a follow-up flexible cystoscopy after 3 months in the outpatient clinic. Maintenance schedules of intravesical chemotherapy, mainly mitomycin C instillations, were given to patients with low-risk bladder cancer but with substantial risk of recurrence. Intravesical immunotherapy with bacillus Calmette-Guérin (BCG) was indicated for intermediate and high-risk bladder cancer patients. At first consultation, patients were randomly assigned to one of the urologists. Most patients underwent transurethral resection multiple times, usually performed by different urologists. Patients with muscle-invasive bladder cancer were scheduled for a cystectomy within a few weeks after the TURBT.

PDD Procedure

To carry out fluorescence diagnosis, patients were instilled with a solution of 1.5 g 5-ALA (Medac GmbH, Hamburg, Germany) in 50 ml 1.4% sodium bicarbonate using a 10F catheter. The PDD procedure was performed under spinal or general anesthesia. Initially the bladder was examined with conventional WLE, followed by inspection under fluorescent light. Resection and cold cup biopsies were carried out under white light. After resection, the completeness of the TURBT was determined under fluorescent light and any areas still fluorescing were resected. A standardized form was used to document the location and fluorescence status of the individual lesions. Data were prospectively collected and entered into the database. Biopsies and resections were classified as fluorescent

‘+’ or ‘−’ and white light ‘+’ or ‘−’. One fluorescent-negative and white light-negative control biopsy was taken from the posterior bladder wall in order to calculate PDD specificity adequately. Occasionally, multiple resections of the same location were taken in case of fluorescent-positive resection borders and deeper resections containing detrusor muscle and put in separate containers for histopathological examination. For statistical analysis, the location of the lesion was recorded only once in the database. In all patients a follow-up WLE was performed after 3 months.

Pathology

All histopathology was revised retrospectively by one pathologist who was blinded to the endoscopic findings. Urothelial carcinomas were graded and staged according to the WHO/ISUP 1998 classification [9] and the UICC/AJC 1992 system.

System Setup

A Karl Storz D-light series was used in white light and blue light mode. An integrated band pass observation filter blocks part of the backscattered blue light resulting in contrast enhancement and improved discrimination between normal blue reflection and suspicious red fluorescent areas. The PDD cystoscope was used in combination with an endoscopic CCD camera (1-chip Urocam, Karl Storz) for the PDD procedures. PDD equipment has not changed considerably during the 10-year period.

Statistical Analysis

Student’s t test and the Mann-Whitney test were used to compare the difference in the number of tumor and false-positive biopsies between surgeon 1 and surgeons 2, 3, 4 and 5. The computer program ‘R’ version 2.6.1 with software library package ‘lme4’ was used for all analyses [10]. A p value <0.05 was considered significant.

Fig. 2. The bars represent time categories (in months) and the number of bladder cancers which recur after PDD-assisted transurethral resection for operator 1 and operators 2, 3, 4 and 5 (42 and 46 procedures, respectively). The numbers in the squares show the number of procedures in the time categories.

Table 2. Mean number of biopsies, tumor biopsies and false-positive results between groups

	Mean number of biopsies	Mean number of tumors	Mean number of false positives
Surgeon 1	4.1	1.81	1.24
Surgeons 2, 3, 4 and 5	3.0	1.27	0.85
p value ¹	<0.001*	0.005*	0.01*
Other surgeons	3.1	1.29	0.70
p value ¹	<0.001*	0.003*	<0.001*

* p < 0.05. ¹ Surgeon 1 is the reference.

The time to recurrence of bladder cancer was determined by calculating the time from one TURBT to the next. Bar charts demonstrate the time to recurrence for both groups.

The learning curve of surgeon 1 illustrates the false-positive rates over time (in months). The learning curve was produced first by plotting the false-positive status of biopsies (y-axis) against time (x-axis) in the chart and second by drawing a line fitted through the scatters using locally weighted scatterplot smoothing (LOESS) [11]. LOESS does this by fitting polynomials to a subset of the data at each point in the data set. 95% confidence intervals are shown in the LOESS plots.

Results

In 280 patients, 1,457 biopsies were taken from fluorescent and nonfluorescent areas. The average number of bladder locations from which biopsies were taken was 3.4 with a range of 1–10 per procedure. Fluorescence cystos-

copy resulted in the resection of 933 fluorescent-positive lesions, of which 391 (42%) were false positive. Fluorescence cystoscopy led to the identification of 97% of the 559 tumors. The sensitivity and specificity of WLE and PDD were 75 and 76%, and 97 and 47%, respectively. The patient characteristics of the study population are shown in table 1. Operators 2, 3, 4 and 5 treated more patients with Ta tumors compared to operator 1 (73% vs. 51%, $p = 0.02$). Operator 1 had more procedures with T2 tumors compared to operators 2, 3, 4 and 5 (19% vs. 6%, $p = 0.007$).

Surgeon 1 took 37% more biopsies (mean 4.1 vs. 3.0, $p < 0.001$), 42% more tumors (1.81 vs. 1.27, $p = 0.005$) and 46% more false positives during PDD (1.24 vs. 0.85, $p = 0.01$) compared to surgeons 2, 3, 4 and 5 combined (table 2). Surgeons 2, 3, 4 and 5 took significantly more false-positive biopsies in WLE (18% vs. 8%, $p < 0.001$).

The mean time to bladder cancer recurrence for all recurrences within 0–18 months was 11.0 months for operator 1 and 8.3 months for operators 2, 3, 4 and 5 ($p = 0.01$, fig. 2). The 3-month recurrence rate in case of any recurrence was 35% for operator 1 and 51% for the other operators ($p = 0.11$).

The false-positive rate of surgeon 1 over time is shown in figure 3. The false-positive rate decreases up to 12–18 months after the first PDD procedure. The false-positive rate between 12 and 18 months is significantly lower compared to the other periods, 28 versus 45% ($p = 0.007$). The false-positive rate between 12 and 18 months for the other 4 surgeons is also lower, 32 versus 43% ($p = 0.07$, data not shown). The mean number of tumors found in the bladder between 12 and 18 months by surgeon 1 is significantly higher compared to overall, 3.3 versus 1.6 tumors ($p < 0.001$). The mean number of tumors found

Fig. 3. Learning curve of operator 1. The LOESS curve shows the false-positive rates of PDD over time, shown with 95% CI (357 fluorescent lesions).

by the other 4 surgeons in the above-mentioned period is also higher, 1.6 versus 1.2 tumors, however this was not significant ($p = 0.11$).

Discussion

Our data show that the urologist appears to be an important factor for the quality of PDD. We found that 1 urologist took more biopsies, found more false positives and resected more tumors compared to the other urologists. Also, the mean time to recurrence of the patients treated by this urologist was significantly increased even though this urologist treated significantly less patients with Ta tumors which, according to the risk table of the European Organization for Research (EORTC), would increase the risk of early recurrences [12].

Some urologists might inspect the bladder more carefully for suspicious areas. These urologists find more false positives, but also resect more tumors leading to more complete TURBTs and longer recurrence times. In accordance, others have found that the false-positive rates vary greatly between institutions [13, 14], 4–53%, which might be the result of a different PDD qualities [15]. Similarly, the rate of tumor residuals found at second look TURBT also varies greatly among hospitals and urologists, 27–78% [16–18]. Many of the residual tumors (54%) are found

outside the primary resection site [19] which would suggest that tumors can be overlooked by urologists.

Residual rates could be prevented by performing flexible cystoscopy and TURBT orderly. First, a bladder diagram and even photo or video documentation is useful to map the bladder and facilitates the resection of the tumors [18]. The use of a bladder diagram has shown to be an independent predictor for lower recurrence rates [20] and is recommended in guidelines for bladder cancer treatment [21]. Second, careful inspection of the entire bladder should be performed at the beginning of the TURBT procedure, even though the bladder has been mapped earlier by flexible cystoscopy. Rod-lens cystoscopy finds approximately 9% additional tumors after inspection with flexible cystoscopy [22]. Most of the lesions missed are <5 mm in diameter. Third, the bladder volume is maintained at 50–75% capacity during TURBT to improve the identification of carcinoma in situ. In addition, overfilling of the bladder increases the risk of bleeding which impairs inspection of the bladder mucosa [16].

The learning curve of the resecting urologists in this study shows a decrease in the number of false positives up to 12–18 months after the first PDD procedure. It has been suggested that limited experience could result in additional false-positive biopsies at the beginning of the learning curve [15]. Urologists might be unsure about the histopathological nature of fluorescent lesions resulting in a more aggressive approach with more false-positive results. Nonmalignant bladder lesions can produce fluorescence but, to our knowledge, the relative fluorescence intensity of false-positive biopsies has not yet been investigated. On the other hand, major variations in PPIX accumulation, with a 10- to 50-fold difference, can be observed in various cell lines [23, 24] which is attributed to a difference in metabolic activity [25].

More tumors were found between 12 and 18 months after the first PDD-assisted TURBT. Fluorescence cystoscopy might have helped the surgeons to better recognize superficial and occult bladder tumors, even during WLE, without the use of blue light cystoscopy. Fluorescence cystoscopy might encourage surgeons to better inspect the bladder with the endoscope close to the bladder wall to search for hidden bladder cancer features.

Surgeon 1 performed more PDD procedures per year and, therefore, might have had more experience and gained more skill. For the other operators, insufficient training and experience might have resulted in poorer outcomes [15]. As others have proposed, dedicated teaching programs for staff members and young residents could improve the quality of the TURBT and reduce the

residual rates after the TURBT [26]. An experienced senior urologist might be needed for teaching in the operating room to improve the quality of the TURBT. Dedicated teaching programs decreased the 3-month recurrence rate from 8 to 3% for staff members and from 28 to 16% for residents. Learning curve programs for PDD-assisted TURBT might be required with experienced surgeons accompanying those with less experience.

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