RESEARCH ARTICLE

Feasibility of Photodynamic Diagnosis for Challenging TUR-Bt Cases Including Muscle Invasive Bladder Cancer, BCG Failure or 2nd-TUR

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Abstract

Background: Despite widely adopted standard methods for follow-up including cystoscopy plus cytology, recurrence rates of non muscle-invasive bladder cancer (NMIBC) have not improved over the past decades, still ranging from 60% through 70%. Hence, widely acceptable surveillance strategies with excellent sensitivity are needed. Early recurrence has led to the development of a novel cystoscopy technique utilizing photodynamic diagnosis (PDD). Although, no studies have evaluated the efficacy of PDD for patients of MIBC, BCG failure or 2nd-transurethelial resection (TUR). Materials and Methods: The present study was performed from October 2012 through May 2013. IRB approved 25 patients initially underwent a cystoscopy examination of white light and blue light followed by the resection of tumors identified. Resections were performed from bladder mucosa areas considered suspicious at PDD, along with PDD negative normal bladder mucosa area resected by random biopsy. Specimens were divided into two groups, PDD positive and negative. Primary endpoints were sensitivity and specificity. Results: A total of 147 specimens extracted from 25 patients were included in the analysis. Some 45 out of 92 PDD-positive specimens were confirmed to have bladder cancer, and 51 out of PDD-negative 55 specimens were confirmed to be cancer negative. The sensitivity of PDD was 91.8% (45/49) and specificity was 52.0% (51/98). The sensitivity:specificity was 89.5% (17/19) : 47.6% (30/63) in 12 2nd-TUR patients, 90.5% (19/21) : 61.1% (11/18) in seven MIBC patients, and 95.0% (19/20) : 48.5% (16/33) in eight failed BCG cases. Conclusions: PDD-TURBT has high sensitivity to diagnose BC even for 2nd-TUR, MIBC or BCG failure cases.

Keywords: Bladder cancer - photodynamic diagnosis - muscle invasive bladder cancer - 2nd-TUR - BCG failure

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Introduction

Bladder cancer is the most common tumor of the urinary tract. Of all cases of bladder cancer, 75% present with non-muscle invasive bladder cancer (NMIBC) that are most often diagnosed using white light cystoscopy (WLC). (Babjuk et al., 2011) NMIBC has a highly variable recurrence rate related to various tumor and host related factors. There is increasing consensus that so called early recurrence may in fact arise from residual tumor left behind at resection or from the growth of previously undetected microscopic lesions. (Brausi et al., 2002; Filbeck et al., 2002; Babjuk et al., 2005; Jocham et al., 2005; Mostafid and Brausi, 2012).

Visual inspection of the bladder with white light is relatively reliable for the detection of papillary tumors, but flat carcinomas such as carcinoma in situ, dysplasia, multifocal growth, and microscopic lesions can be overlooked or inadequately resected. Photodynamic diagnosis (PDD) has been developed as a novel technique aiming better detection rate compared to conventional modalities. Two drugs have been utilized to diagnose bladder cancer by PDD: 5-aminolevulinic-acid (5-ALA) and its derivate hexyl aminolevulinate (HAL; Hexvix Photocure, Oslo Norway). PDD is a technique which uses blue light cystoscopy (BLC) to enhance the visual contrast between benign and malignant tissue, especially carcinoma in situ, by selective accumulation of red-fluorescent porphyrins, mainly protoporphyrin IX (PpIX). Recent studies suggest that PDD may improve diagnostic sensitivity, reduced residual tumor rates, and prolonged recurrence-free survival (RFS) for NMIBC. Sensitivity and specificity of WLC and PDD are 46%-80% and 76-97%, and 43%-98% and 35-66%, respectively. (Zaak and Hofstetter, 2002; Grimbergen et al., 2003; Jichlinski et al., 2003; Schmidbauer et al., 2004; Fradet et al., 2007;

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Grossman et al., 2007; Jocham et al., 2008; Stenzl et al., 2008; Geavlete et al., 2012) Now PDD is emerging to diagnose NMIBC or carcinoma in situ. However no studies specifically used PDD for muscle invasive bladder cancer, cystoscopic observation for BCG failure cases or 2nd-TUR cases. In the present study, challenging cases for complete tumor resection in daily clinical practice were selected for PDD-assisted TUR. Patients selected for the study were those with MIBC, high-grade T1-2 flat tumor with/without carcinoma in situ, who had positive urine cytology after BCG instillation, or who received 2nd-TURas a pathological assessment after primary TURBT with curative intent. We first attempted to evaluate the feasibility of PDD-assisted TUR for these annoying cases. Thereafter, sensitivity and specificity of PDD were confirmed.

Materials and Methods

The study was performed between October 2012 and May 2013. The present study was fully approved by IRB. 25 patients were contained in the study. Patients with histologically proven bladder urothelial carcinoma more than pT1or more than cT1 were included in the study. Inclusion criteria for the present analysis were as follows: Patients with MIBC, high-grade T1-2 flat tumor with/without carcinoma in situ, short- or mid-term positive urine cytology after BCG instillation, or those who received 2nd-TUR as a pathological assessment after primary TURBT with curative intent - those deemed to be clinically hard to fulfill complete tumor resection in daily practice. All contributors took 5-aminolevulinic acid (40mg/kg) dissolved in 50 ml of 5% glucose 3 hours prior to PDD-assisted TURBT. We utilized Karl Storz Photodynamic Diagnostic D-Light C = PDD System.

All patients initially underwent cystoscopy examination of white light and blue light followed by the resection of the tumors identified. Resections of bladder tumors were performed starting from bladder mucosa areas considered suspicious at PDD cystoscopic examination to visible tumors with WLC, along with PDD negative normal bladder mucosa area resected by random biopsy. Resected sections were divided into two groups of PDD positive (areas shining in red by PDD = fluorescent-positive) and PDD negative (random biopsy areas). All specimens were subjected to central pathology review and evaluated by two specialists. Primary endpoint of the study was sensitivity and specificity. Chi-squared tests were used to analyze associations between categorical variables, and the student's t-test was used for continuous variables. Univariate and multivariate logistic regression were used to assess each of variables as predictors of pathological diagnosis. All statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, Illinois).

Results

The 25 patients (20 males and 5 females) were included in this study. The mean age was 66.3 years (range, 50 to 88). Six patients were obese (BMI>25) and 19 patients were not (BMI<25). The 14 patients had having smoking history (Brinkman Index>400) and 11 patients had not (Brinkman Index<400). The 15 patients had preoperative microscopic hematuria and 10 patients did not. Seven patients were diagnosed to be MIBC. Of all patients, 3 patients (12.0%) were TURBT naive, while 22 patients (88.0%) received TURBT more than two times. The 12 patients (52.0%) received PDD-TUR as 2nd-TURBT. Among those, 8 patients (66.7%) were viable cancer positive. Three patients who received TURBT for the first time proved to be newly diagnosed bladder cancer and two were MIBC, one were UC with CIS. The 14 patients (56.0%) received prior therapy, including bladder preservation therapy such as BCG, radiation or BOAI-therapy. Eight patients (32.0%) were BCG failure. Table 1 shows the patient characteristics of the study population. In 25 patients, we extracted 147 specimens Including 92 fluorescent-positive specimens and 55 non-fluorescent-positive specimens. Of those, 19 specimens (12.9%) were with concomitant CIS, and 26 specimens (17.7%) were with MIBC. By comparison between two groups using t-test, no differences were found between the PDD positive group and the PDD negative group in age (p=0.860), gender (p=0.242), BMI (p=0.165), and Brinkman Index (p=0.237). 18.5% of fluorescent-positive specimens that were diagnosed carcinoma in situ prone to have sensitivity compared to 3.6% of non-fluorescent specimens (p<0.010). Among 92 fluorescent positive specimens, 45 cases were confirmed to have a bladder cancer. Thus the positive predictive value of BLC in the diagnosis of bladder cancer was 48.9%. The 55 non-fluorescent portions, which were suspicious by WLC, were also resected. After pathological examination of these lesions, 51 cases had proved to be benign. Only 4 of those were diagnosed urothelial carcinoma. Two of them were diagnosed to have concomitant carcinoma in situ. Thus, the negative predictive value of BLC in the diagnosis of bladder cancer was 92.7%. Among 49 specimens, diagnosed to be an urothelial carcinoma, 45 were fluorescent positive specimens. Therefore sensitivity of BLC in the diagnosis of bladder cancer was 91.8%. Among 98 specimens of bladder mucosa, 51 were non-fluorescent. Therefore specificity of BLC was 52.0%. The false positive rate of fluorescence diagnosis was 48.0%

Table 1. Baseline Characteristics of All Patients

Characteristic		Value
Number of patients		25
Age		66.3(55-88)
Gender	Male	20
	Female	5
Body mass index	25>	19
	≥25	6
Brinkman Index	400>	11
	≥400	14
Preope hematuria	Negative	10
	Positive	15
Operation contents	First time	3
	2nd-TUR	12
	BCG failure	8
	Effect measurement	2

Preope hematuria: preoperative hematuria

(47/98). The 88.9% (16/18) of CIS lesions were detected by PDD. On univariate analysis, preoperative microscopic hematuria (OR 2.28, 95%CI 1.23, 6.45; p=0.014), and PDD (OR 12.20, 95%CI 4.80, 36.56; p<0.001) were predictors of pathological diagnosis. On multivariate analysis, gender (OR 0.33, 95%CI 0.11, 0.97; p=0.044), preoperative microscopic hematuria (OR 3.24, 95%CI 1.20, 8.72; p=0.020), and PDD (OR 12.20, 95%CI 3.90, 38.13; p<0.001) were predictors of pathological diagnosis.

The 12 patients received PDD-TUR as 2nd-TUR, 8 patients received PDD-TUR after BCG therapy and 7 patients were diagnosed MIBC by PDD-TUR. The 50 fluorescent positive specimens and 32 non-fluorescent specimens in 2nd-TUR, the 35 fluorescent positive specimens 18 non-fluorescent specimens in failed BCG therapy, and the26 fluorescent positive specimens and 13 non-fluorescent specimens in MIBC were resected, respectively. We recognized asignificant difference in the diagnosis of CIS between PDD positive group where and negative group in patients failed BCG therapy; 31.4% of fluorescent-positive vs. 5.5% of fluorescent negative, p =0.041 in. Among 17 specimens diagnosed as urothelial carcinoma, 15 were fluorescent positive specimens in 2nd-TUR, 19 out of 20 specimens diagnosed urothelial carcinoma were fluorescent positive in failed BCG therapy, and 19 out of 21 specimens of UC were fluorescent positive specimens in MIBC. Therefore, sensitivity of BLC in the diagnosis of bladder tumor in

Table 2. Characteristics of PDD Positive and Negative Groups

	Specimens of all Patients			Specimens of Patients who Received TUR as 2nd-TUR			Specimens of Patients who were BCG Failure			specimens of patients who were MIBC		
	PDD positive (N=92)	PDD negative (N=55)	P value	PDD positive (N=50)	PDD negative (N=32)	P value	PDD positive (N=35)	PDD negative (N=18)	P value	PDD positive (N=26)	PDD negative (N=13)	P value
Age	66.3 (50-88)	66.1 (50-88)	p=0.860	65.9 (51-88)	65.6 (51-88)	p=0.848	64.8 (51-77)	67.2 (51-77)	p=0.356	66.3 (50-88)	66.1 (50-88)	p=1.000
Gender												
Male	20	17		8	9		28	13		15	8	
Female	72	38	p=0.242	42	23	p=0.264	7	5	p=0.730	11	5	p=0.818
Body mass index												
25>	31	25		27	19		0	0		14	10	
≥25	61	30	p=0.165	23	13	p=0.656	35	18	-	12	3	p=0.295
Brinkman Index												
400>	39	29		24	18		0	0		5	5	
≥400	53	26	p=0.237	26	14	p=0.504	35	18	-	21	8	p=0.253
Preope hematuria												
Negative	25	22		13	6		17	13		1	1	
Positive	67	33	p=0.143	37	26	p=0.593	18	5	p=0.145	25	13	p=1.000
carcinoma in situ												
Negative	75	53		44	32		24	17		24	13	
Positive	17	2	P=0.010	6	0	p=0.077	11	1	P=0.041	2	0	P=0.544
Pathology												
Negative	47	51		33	33		16	17		7	11	
Positive	45	4	P<0.001	17	2	p=0.003	19	1	P=0.001	19	2	P=0.002
Initial Grade												
low	-	-	-	7	9		17	5		-	-	-
high	-	-	-	43	23	p=0.155	18	13	P=0.239	-	-	-

Preope hematuria: Preoperative hematuria, Pathology of first transurtheral resection, PDD: photodynamic diagnosis

Table 3. Multivariable Analysis of Predictors of Pathological Diagnosis

	Specimens of All Patients			Specimens of Patients who Received TUR as 2nd-TUR			Specimens of Patients who were BCG Failure			Specimens of Patients who were MIBC		
Covariate	Hazard Ratio	P value	95%CI	Hazard Ratio	P value	95%CI	Hazard Ratio	P value	95%CI	Hazard Ratio	P value	95%CI
Gender												
	0.33	0.044	0.11-0.97	0.53	0.549	0.07-4.29	0.23	0.249	0.02-2.81	0.51	0.670	0.23-11.35
Body mass index(25> *vs* ≥25)												
	1.36	0.518	0.57-3.44	0.20	0.186	0.02-2.19	-	-	-	6.59	0.128	0.58-74.88
Brinkman Index(400> *vs* ≥400)												
	2.43	0.057	0.98-6.08	2.02	0.430	0.35-11.66	-	-	-	1.16	0.939	0.03-51.34
preoperative hematuria												
	3.24	0.020	1.20-8.57	1.88	0.560	0.22-15.80	0.97	0.977	0.13-7.35	0.23	0.566	0.01-33.64
Photodynamic diagnosis												
	12.20	<0.001	3.90-38.13	8.12	0.011	1.62-40.73	27.87	0.008	2.36-328.57	16.18	0.005	2.27-115.17
Initial Grade (low *vs* high)												
	-	-	-	2.54	0.379	0.32-20.18	0.23	0.085	0.04-1.22	-	-	-

2nd-TUR, failed BCG therapy and MIBC was 89.5%, 95.0% and 90.5%, respectively. We conducted the logistic regression.analyses to evaluate the significance of the factor which participated in pathological diagnosis On univariate analysis, PDD was the significant factor for pathological diagnosis.. Moreover, on multivariate analysis, PDD (OR 8.12, 95%CI 1.62, 40.73; p=0.011/ OR 27.87, 95%CI 2.36, 328.57; p=0.008/ OR 16.18, 95%CI 2.27, 115.17; p=0.005) were the only predictor of pathological diagnosis in 2nd-TUR, failed BCG therapy and MIBC, respectively. Table2 showed characteristics of PDD positive and negative groups and Table3 showed multivariable analysis of predictors in pathological diagnosis.

Discussion

Accumulating evidence supports that PDD offers improved tumor detection, reduced residual tumor rates after TURBT, and prolonged recurrence-free survival (RFS) for NMIBC. (Riedl et al., 2001; Zaak et al., 2001; Daniltchenko et al., 2005) Most of the previous studies test the pTa, maximally pT1 NMIBC patients. However no studies so far specifically used PDD for 2nd-TUR for muscle invasive bladder cancer (MIBC) and for BCG failure. We, for the first time, reported the application of PDD-TUR for cases of MIBC, post-BCG, or concomitant CIS. Sensitivity and specificity of PDD in our study were 91.8% and 52.0%, respectively. In recent studies, sensitivity and specificity of PDD for NMIBC range from 76% to 97% and 35% to 66%, respectively. The present study focused only for ≥pT1 patients and showed that sensitivity of PDD-TUR was 92.1%, showing the noninferiority of PDD for ≥pT1 cases to PDD for >pT1cases.

CIS tends to progress to invasive cancer and requires complete resection, but it is not easily to detect CIS under WLC, hence CIS is a favorable target of PDD. Fradet et al. describes that CIS detection rate of 92.0% for BLC is superior to WLC, which diagnosed only 68% of the CIS lesions. (Fradet et al., 2007) Zaak et al. showed similar results of a CIS detection rate of 91.2% for BLC and 47.2% for WLC. (Zaak and Hofstetter, 2002) Likewise, our study showed that 89.9% (17/19) of CIS lesions were detected by BLC.

The rates of cancer detection found at the time of a 2nd-TUR vary in the literature from 20% to 81.5%. Thus, we strongly encourage the use of PDD for restaging TUR, not only for a more accurate pathological confirmation but also for its therapeutic effect. In order to achieve minimal tumor burden, it is important that the highest quality TUR be performed for all patients for both initial diagnosis and restaging. Quality control for TUR put forward inspection of the surgeon's macroscopic resection to ensure no visible tumor is remaining, to identify the presence of muscle in the final specimen. Divrik et al found that in a prospectively randomized trial patients either receiving a single TUR or a 2nd-TUR, found 5-year recurrence-free survival rates of 32% and 59% (p<0.001), respectively. (Divrik et al., 2010) 2nd-TUR is recommended for any high-grade NMIBC detected at the initial TUR. However no studies specifically used PDD for 2nd-TUR, which may help guide surgeon for better visualization of the residual tumor by the BLC. The present study showed that PDD-TUR for 2nd-TUR had feasibility in sensitivity and specificity. PDD may improve RFS by the decrease in residual tumors in concert with 2nd-TUR.

The main limitation of PDD is the relatively high false-positive detection rate which ranges from 12% to 26%. (Grimbergen et al., 2003; Stenzl et al., 2010; Hermann et al., 2011) In present study, false-positive cases were related with recent TURBT history, the use of BCG, and urinary tract infection. In this study, the false positive rate of fluorescence diagnosis was 48.0% (47/98). The overall false positive rate in the present study is higher than the other studies because of the nature of the present study which contained the patients that received 2nd-TURBT within a half year, or bladder preservation therapy such as radiation or BOAI-therapy, otherwise post BCG instillation setting. When 2nd-TURBT cases and bladder preservation therapy cases were picked and specifically evaluated for the false-positive rate, it turned out to be lesser as 31.3%, double checking the difficulty of detection malignant legions from these challenging cases.

Intravesical BCG treatment is currently the standard of care for patients with high-grade NMIBC and CIS. BCG reduces cancer recurrence by 40%, compared with TUR alone, and also reduces progression, unlike other intravesical chemotherapeutic agents. (Fradet et al., 2007) Although BCG is the most effective treatment, roughly 50% of patients still experience a recurrence within 5 years. (Morales, 1984; Sylvester et al., 2002; Brausi et al., 2011) The American Urological Association guidelines currently recommend radical cystectomy as first line therapy in patients who fail BCG. The European Association of Urology guidelines state that a patient has failed BCG when a patient develops MIBC, or when high-grade NMIBC is present at both 3 and 6 months after BCG instillation. They also recommend cystectomy as the next line of treatment in early BCG failure (in patients who can tolerate it) because of the increased risk of developing MIBC. National Comprehensive Cancer Network guidelines also recommend early cystectomy for patients with recurrence after BCG, although these guidelines do not clearly define BCG failure. Early cystectomy is widely recommended because it is superior in the oncologic control of BCG-refractory bladder cancer. Leibovici D et al. reported that, TUR monotherapy is appropriate for the treatment of patients with T2N0MX bladder cancer for whom local endoscopic resection is likely to produce complete removal of the tumor exclusive of concomitant noninvasive disease. (Leibovici et al., 2007) Patients with loco regional extension of disease as evidenced by hydronephrosis or lymphadenopathy on axial imaging are not good candidates for this approach. Sensitivity of PDD-TUR in patients who fail BCG was high as 95.0% in this study, which may contribute to reduce the need for cystectomy by reducing residual tumors especially in patients who are not fit for cystectomy, refuse cystectomy, are old age, or have low-grade recurrence after BCG.

Observation period was short and primary endpoint of the study was sensitivity and specificity, we cannot

appraise survival benefit. Continuous long term follow-up is necessary to determine whether PDD prolonged RFS of patients who received PDD-TUR as 2nd-TUR by reducing residual tumor rate.

In conclusion, this study suggests that PDD for 2nd-TUR, MIBC, and BCG failure has feasibility and is predictor of pathological diagnosis. PDD-TUR for 2nd-TUR, MIBC, and BCG failure is a potential bladder-sparing treatment option for selected patients.

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