

# Comparative study of screening techniques used in early detection of urinary bladder cancer

## Abstract

**Background:** Early detection of urinary bladder cancer can help improve patients' outcomes. Detection and follow-up for recurrence by cystoscopy and histopathology of obtained biopsies is costly and causes discomfort to patients. There is a need to find sensitive, specific screening techniques as alternatives to reduce the frequency or to improve the sensitivity for detection of early bladder cancer.

**Objective:** This study aimed to compare bladder washing cytology (BWC), bladder tumor antigen (BTA), flowcytometry (FCM), and photodynamic diagnosis (PDD) for early detection of urinary bladder cancer.

**Methods:** This prospective cohort study was conducted on 75 patients with hematuria/cystitis or previous resection of bladder cancer. The four diagnostic techniques were performed in every patient. The results of the studied techniques were compared to the histopathological findings in these patients. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated.

**Results:** The BWC and PDD showed the highest accuracy (each was 77.3%). The PDD technique had the highest sensitivity and NPV (91.3% and 94.9%, respectively), while the BWC had the highest specificity and PPV (92.3% and 71.4%, respectively). Sensitivity was higher in high grade tumors than the low grades in BWC, while sensitivity was higher in the low-grade tumors than the high grades in the other techniques.

**Conclusions:** The BWC and PDD had the highest accuracy for detection of bladder cancer. Their combined use is recommended to obtain high sensitivity and specificity.

**Keywords:** bladder wash cytology, bladder tumor antigen, flowcytometry, photodynamic diagnosis, urinary bladder cancer

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**Abbreviations:** BWC, bladder washing cytology; BTA, bladder tumor antigen; FCM, flowcytometry; PDD, photodynamic diagnosis; NPV, negative predictive value; PPV, positive predictive value; CIS, carcinoma in situ; CT, computed tomography; TURBT, transurethral resection of superficial bladder tumor

## Introduction

An important step in the management of the urinary bladder cancer is early detection before progression into invasive cancer if left untreated.<sup>1</sup> Screening for bladder cancer in patients who present with hematuria or with irritative voiding symptoms is mandatory.<sup>2</sup> Unfortunately, the sensitivity of voided urine cytology is 30% in low grade disease. Thus, the development of highly sensitive urinary tests for the detection of bladder cancer is required to avoid delayed management and improve patients' outcomes.<sup>3</sup> Screening techniques are required to have acceptable sensitivity, specificity as well as positive and negative predictive values. A test with false positive result may lead to unnecessary expense and possible morbidity. Alternatively, a test with false negative result may deceive patients and their physicians with a false sense of security that may delay the diagnosis of cancer.<sup>4</sup> Some promising screening techniques

were developed for detection of bladder cancer. Urine cytology is considered for the detection of flat TCC and carcinoma in situ (CIS) lesions that may go unrecognized by cystoscopy. However, cytological preparations are more sensitive for detecting the higher-grade lesions. Urine cytology is of benefit before cystoscopy in highly suspicious cases without obvious lesions by pelvic ultrasound or computed tomography (CT).<sup>5</sup> The bladder tumor antigen (BTA) test detects basement membrane degradation fragments, which occur mainly in invasive disease.<sup>6</sup> Flowcytometry (FCM) detects DNA aberrations (polyploidy or aneuploidy) that may appear at an early stage of the tumor development and before recognizable changes in morphology.<sup>7</sup> Photodynamic diagnosis (PDD) of neoplastic urothelial bladder is an approach in which hexaminolevulinic acid is instilled locally in the bladder as a photosensitizer that can be used to label bladder tumors. This technique is particularly useful to reveal areas of dysplasia, CIS and micro papillary tumor.<sup>8</sup> The aim of the present study was to compare the results of some screening tests for urinary bladder cancer (including urine cytology, BTA, FCM, and PDD) with the histopathological examination results of suspicious areas in screened at risk patients.

## Methods

### Ethical considerations

The study protocol was approved by the Research Ethics Committee of the National Institute of Urology and Nephrology, Cairo, Egypt. Informed written consent was obtained from each patient. Patients' data were kept anonymous.

### Study settings

This study was conducted on 75 patients who attended urology clinic during the period from January 2017 to February 2019.

### Eligibility criteria

The study included patients of either sex who were 18- years-old or above and presented with one of the following: a) persistent cystitis (after exclusion of urinary TB and urinary tract infection); b) hematuria (with no manifested cause); and c) transurethral resection of superficial bladder tumor (TURBT) or precancerous lesions.

### Preliminary evaluation

All patients were subjected to initial evaluation, including a full history taking, meticulous general and abdominal examination, and bimanual digital rectal or vaginal examination. Investigations included urine analysis, full blood picture, blood sugar level, liver enzymes, prothrombin time and concentration, serum creatinine, blood urea level, the excretory urography (IVU), abdominopelvic ultrasonography and CT.

### Bladder wash cytology (BWC)

A bladder wash sample was obtained prior to cystoscopy by rinsing the urinary bladder at least twice with 50cc saline solution. Part of the bladder wash sample was used for routine cytological examination by a pathologist. Each sample was cytologically scored as negative, atypia, low-grade or high-grade cancer.

### Bladder tumor antigen (BTA) test

A voided urine sample was collected for BTA stat test after urinary tract infection was excluded. The patient's urine was added to the BTA test stat and allowed to react with the control zone and patient zone. In the patient (p) zone, antigen-conjugate complexes are captured by a second antibody forming a visible line. In the absence of the antigen in the patient urine, no visible line is formed. The control zone contains an immobilized reagent, which will capture the conjugate independently in the presence or absence of the antigen, thereby allows producing a line. This procedural control assures the operator that the device is working properly.

### Flowcytometry (FCM)

Before cystoscopy, the bladder was washed vigorously 6 or 7 times through a Nelaton catheter using approximately 200 ml saline. The samples were centrifuged, then suspended in phosphate buffered saline followed by a second centrifugation and fixation in 50% ethanol, staining with propidium iodide and analysis with FCM equipped with an argon laser light beam (wavelength 488 nm).<sup>9,10</sup> For histograms with less than 10,000 cells, at least one clearly identifiable peak had to be present to consider the analysis interpretable. Samples not meeting these criteria were rejected.<sup>11</sup>

### Photodynamic diagnosis with fluorescence detection

Cystoscopy was performed after intravesical instillation of hexaminolevulinic acid in patients with suspected primary or recurrent bladder cancer. Two to three hours before planned cystoscopy a neutral solution was prepared to contain 1.5gm of hexaminolevulinic acid dissolved in 50ml 2.4% sodium bicarbonate. This freshly prepared solution was instilled via 12-French catheter after evacuation of the bladder, and the catheter was then removed. The patient was asked to change his position regularly to obtain sufficient mucosal contact of the entire bladder surface.<sup>12</sup> The dosimetry light system was used for fluorescence diagnosis. It consists of a light source with a xenon arc lamp and a corresponding band pass filter with a wave length of 380 to 450 nm. By switching the foot pedal, the filter was placed or removed and either blue or standard white light was produced.<sup>13</sup> The urinary bladder was first inspected under white light before exposure to blue light and every fluorescence positive area was once more inspected with a white light and macroscopic appearance was noted. Cold biopsies were taken from every fluorescent area, every macroscopically suspicious non-fluorescent area, and at least two normally appearing non-fluorescent zones. Hypervascularized erythematous, erosive or edematous areas of mucosa were considered non-specifically inflamed.

### Statistical analysis

Data were collected and analyzed using Statistical Package for Social Sciences, version 22. Numerical variables with normal distribution were summarized as mean±standard deviation. Categorical variables were summarized as frequencies. Sensitivity, specificity, NPV, and PPV for each score were determined in relation to histopathological examination of biopsies.

## Results

Seventy-five patients (56males and 19females) with manifestations of superficial urinary bladder cancer or previously treated with TURBT were included in this study. The mean age of patients was 41.2 years for males and 42.2 years for females. Histopathological examination revealed that the urinary bladder lesions were benign in 52 patients (69.3%) and malignant in 23 patients (30.7%). The malignant lesions were of low grade in 13 patients (17.3%), high grade in six patients (7%), and invasive in four patients (5.3%) (Table 1). The results of the studied screening tests were compared to the findings of histopathological examination and accordingly the frequencies of true positive, false positive, true negative and false negative results of each test were recorded. A positive result of a test indicates a malignant lesion, while a negative result indicates a benign lesion. From these data, sensitivity, specificity, PPV, NPV, and overall accuracy of each test were calculated (Table 2). The techniques with the highest overall accuracy were BWC and PDD (each was 77.3%). The PPD technique had the highest sensitivity and NPV (91.3% and 94.9%, respectively), while the BWC had the highest specificity and PPV (92.3% and 71.4%, respectively). The sensitivity of each screening technique was also studied in relation to the grading of the malignant lesion (Table 3). For BWC, the sensitivity was 30.8%, 50%, and 75% in low, high grade, and invasive lesions, respectively. For BTA, the sensitivity was 84.6%, 66.7%, and 100% in low, high grade, and invasive lesions, respectively. For FCM, the low number of true positive results interferes with the interpretation of the sensitivity in different grades of malignancy. For PDD, the sensitivity was 92.3%, 100%, and 75% in low, high grade, and invasive lesions, respectively.

**Table 1** Distribution of sex and age of the studied cases

Patients' characteristics (total n = 75)			
Sex <sup>a</sup>			
	Females	19	25.3
	Males	56	74.7
Age (years) <sup>b</sup>			
	All patients	41.8 (17-84)	
	Females	42.2 (17-70)	
	Males	41.2 (17-84)	
Histopathology findings <sup>a</sup>			
Benign		52	69.3
Malignant		23	30.7
Low Grade	Dysplasia	10	13.3
	TaGI	3	4
High Grade	TaGIII	3	4
	T1GII	2	2.7
	T1GIII	1	1.3
Invasive	T2GII	3	4
	T3GII	1	1.3

a: number and percentage; b: mean (range)

**Table 2** The sensitivity, specificity, positive and negative predictive values of the studied screening techniques for detection of malignant urinary bladder lesions in the study patients

	The studied screening techniques			
	BWC	BTA	FCM	PDD
True positive results (n)	10	19	4	21
False positive results (n)	4	32	5	15
False negative results (n)	13	4	19	2
True negative results (n)	48	20	47	37
Sensitivity (%)	43.5	82.6	17.4	91.3
Specificity (%)	92.3	38.5	90.4	71.2
PPV (%)	71.4	37.3	44.4	58.3
NPV (%)	78.7	83.3	71.2	94.9
Overall accuracy (%)	77.3	52	68	77.3

BWC, bladder wash cytology; BTA, bladder tumor antigen; FCM, flowcytometry; PDD, photodynamic diagnosis; n: number; PPV, positive predictive value; NPV, negative predictive value

**Table 3** The sensitivity, specificity, positive and negative predictive values of the studied screening techniques for detection of malignant urinary bladder lesions in the study patients

Histopathology		Total number	BWC		BTA		FCM		PDD	
			TP(n)	Sensitivity (%)	TP(n)	Sensitivity (%)	TP(n)	Sensitivity (%)	TP(n)	Sensitivity (%)
Low Grade	Dysplasia	10	2	20	9	90	0	0	9	90
	TaGI	3	2	66.7	2	66.7	1	33.3	3	100
	Total	13	4	30.8	11	84.6	1	7.7	12	92.3
High Grade	TaGIII	3	1	33.3	3	100	1	33.3	3	100
	T1GII	2	2	100	0	0	1	50	2	100
	T1GIII	1	0	0	1	100	0	0	1	100
	Total	6	3	50	4	66.7	2	33.3	6	100
Invasive	T2GII	3	2	66.7	3	100	1	33.3	3	100
	T3GII	1	1	100	1	100	0	0	0	0
	Total	4	3	75	4	100	1	25	3	75

BWC, bladder wash cytology; BTA, ladder tumor antigen; FCM, Flowcytometry; PDD, photodynamic diagnosis; TP, true positive

## Discussion

In the present study, we compared four of the most commonly used screening techniques to detect bladder cancer. The BWC is popularly used as it is superior to both voided urine sample (due to its hypercellularity) and catheterized sample (due to better preservation of cells).<sup>14</sup> The sensitivity of BWC for detection of malignant lesions was 43.5% and the specificity was 92.3%. The sensitivity of BWC was 30.8% in low grade tumors, 50% in high grade tumors, and 75% in invasive tumors. These results were in partial agreement with those of Kranzbühler et al.<sup>15</sup> who found that the overall sensitivity and specificity were 16% and 99%, respectively. The sensitivity was 13% for low grade, and 20% for high grade disease. In this study, the overall sensitivity of BTA test was 82.6%, meanwhile the sensitivity of the test was 84.6%, 66.7%, and 100% for low grade, high grade, and invasive tumors, respectively. Other studies reported an overall sensitivity ranging from 56% to 83% sensitivity.<sup>16-20</sup> This great variability of the results might be caused by differences in sample size, the proportion of new cases versus recurrent tumor as well as grades and stages of the tumors. The specificity of BTA test in our study was 38.5%, which is much lower than that reported previously (72% - 92%).<sup>16-20</sup> This lower specificity could be attributed to the high frequency of false positive results in our study that may have been caused by the intravesical instillation of BCG in 32 cases before starting the study. In addition, the presence of benign schistosomal lesions or chronic bladder disease may cause false positive results. Similarly, Raitanen<sup>17</sup> reported that the specificity of BTA test dropped in patients treated with BCG due to BCG-induced local inflammatory effect.

The relatively high false positive result rates may be explained by the fact that urine samples may be extremely hypocellular in some patients with bladder neoplasms.<sup>7</sup> Moreover, false positives may occur due to hematuria as human complement factor H-related protein is present in blood. Urological conditions that may present with hematuria – and thus give rise to false positive results – include urolithiasis, recent instrumentation, inflammation, other genitourinary malignancies, and BCG therapy -induced cystitis.<sup>18,21</sup> Therefore, the use of BTA tests cannot be recommended for use in clinical practice as its results showed low sensitivity and high rates of false-positive results.<sup>22</sup> Our study revealed that the overall sensitivity of FCM analysis was 17.4%. The sensitivity of FCM analysis for low grade bladder cancer was 7.7% and for high grade non-invasive bladder cancer was 33.3%. However, its sensitivity for invasive bladder cancer decreased to 25% because we have 2 cases with persistent hematuria, which makes the test invalid. Meanwhile, the overall specificity of FCM analysis in our study was 90.4%.

The sensitivity of FCM- as reported by previous studies - varied widely according to the tumor grade. The sensitivity of FCM ranged from 12% to 70% in low grade tumors and from 45% to 89% in high grade tumors.<sup>11</sup> This is attributed to the cut off values for determining significant hyper-diploid fraction, which vary from 7% to 12% in these studies. This indicates the limited diagnostic value of DNA -FCM on bladder washing in case of low grade and low stage tumors.<sup>4</sup> Similar disappointing results with diagnostic DNA FCM were reported.<sup>23</sup> In patients with CIS, cytology and FCM are helpful in the diagnosis of these high grade lesions with a sensitivity of more than 90%.<sup>24</sup> The most frequent types of bladder cancer among our patients were low grade and of early stages. Consequently, FCM was of little value in screening for early detection of bladder cancer as it has usually

diploid DNA content. In addition, intravesical chemotherapy and immunotherapy with BCG induce hypocellularity and inflammatory reaction that decrease the accuracy of FCM.<sup>23</sup> Fluorescence cystoscopy using PPD can detect neoplastic and pre-cancerous lesions among areas of healthy tissue, allowing more accurate sampling for histopathological examination and enabling removal of the tumor with an appropriate safety margin.<sup>25</sup> In the current study, the overall sensitivity of PDD was 91.3%. This is compatible with the results of previous studies that reported a range from 92% to 100%.<sup>26,27</sup> The sensitivity of PDD for low grade tumors and dysplasia was 92.3, which is comparable to the results of Witjes et al.<sup>8</sup> and Ray et al.<sup>28</sup> (94% and 95%, respectively). The sensitivity of PDD for high grade bladder tumors was 100%, which is compatible with earlier studies.<sup>8,13</sup>

The sensitivity of PDD in our study was affected by a case of invasive bladder tumor that gave false negative result by PDD. This could be explained by the concealment of this lesion under a non-fluorescent fibrous scar following radiotherapy received before our examination. Sakel et al.<sup>12</sup> demonstrated limitation of PDD after previous radiotherapy or at the previous TURBT site during secondary TURBT as they found its sensitivity to be 81% in their group of patients undergoing secondary TURBT. Unfortunately, a high incidence of false positive results has been found in the current study that decreased specificity in our series of patients to 71.2%, which is comparable to the results of Kriegmair et al.<sup>29</sup> (66% to 78%). The high percentage of false positives is mainly due to accumulation of the photosensitizer in tissues during inflammation. Aboumarzouk et al.<sup>30</sup> reported a high percentage of false positives within less than 3 months following intravesical administration of BCG and after recent bladder resections. The data present in our study revealed that the best diagnostic tests were the BWC and PDD as both tests attained an overall accuracy of 77.3%. The BWC had the highest specificity and PPV, while PDD had the highest sensitivity and NPV. These findings suggest that the combined use of both tests may be more helpful in early diagnosis of bladder cancer. In the current study, it was found that the overall sensitivity for BWC was 43.5% versus 82.6% for BTA test. This increased sensitivity of BTA test over BWC is more apparent in the lower grade tumors (84.6% Vs 30.8%, respectively). On the other hand, this difference diminished slightly but was still apparent for high grade tumors (66.7% vs 50% for BTA test and BWC respectively). The sensitivities of FCM for low grade, high grade, and invasive bladder cancer were 7.7%, 33.3%, and 25%, respectively.

## Conclusion

In conclusion, bladder wash cytology and BTA test are helpful in diagnosing high grade carcinoma, whereas low grade tumors often reveal false negative results. However, PDD-guided biopsies can be helpful for detecting low grade tumors. The combined use of BWC and PDD seems to provide the best results among the four studied techniques. Future studies with larger sample sizes are recommended to confirm the accuracy of each test with respect to the tumor grade and stage.

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## Conflicts of interest

The author declares there is no conflict of interest.

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