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Effect of blue-light cystoscopy on contemporary performance of urine cytology

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Objective

To evaluate the performance of urine cytology based on contemporary data, including the effect of enhanced cystoscopic techniques.

Materials and Methods

Individual patient data were obtained from three prospective studies: the Photocure (PC) B305 and the PC B308 studies, evaluating the use of blue-light cystoscopy with hexaminolevulinate (BLC-H), and the Cxbladder monitoring study, evaluating the Cxbladder monitor test for the detection of recurrent urothelial carcinoma. The specificity and sensitivity of cytology in each study and for the overall cohort were calculated.

Results

A total of 1 487 urine samples from 1 375 patients were included in the analysis; overall 615 tumours were detected correlating to 41% of the cytological specimens. The pooled sensitivity and specificity for cytology were 40.8% and 92.8%, respectively. The pooled sensitivity was 11.4% for low-grade/World Health Organization (WHO) grade 1 disease and 54.3% for high-grade/WHO grade 3 disease. There were no differences in cytology sensitivity based on the type of cystoscopy used, with sensitivity of 41.3% and 40.4% in white-light cystoscopy (WLC) and BLC-H, respectively. Subgroup analysis including carcinoma *in situ* (CIS) showed a trend towards lower cytology sensitivity in BLC-H (54.5%) vs WLC (69.2%).

Conclusions

Based on analysis of contemporary data, the sensitivity of cytology for detecting high-grade tumours and CIS remains low. On a per-patient analysis, cytology sensitivity was not affected by the use of advanced cystoscopic techniques except in patients with CIS. The use of cytology as the main adjunct to cystoscopy in patients at high risk can lead to missed opportunities for early detection of recurrence and for determining which patients are not responding to intravesical therapies such as bacille Calmette-Guérin.

Keywords

Cxbladder, cytology, blue-light cystoscopy, carcinoma *in-situ*, fluorescence cystoscopy, urine cytology, #BladderCancer, #blcsm, #uroonc, #urology

Introduction

Urothelial carcinoma of the bladder (UCB) is one of the most common urological malignancies, with an estimated incidence of >81 000 cases in the USA during 2018 [1]. Over 75% of those cases are diagnosed as non-muscle-invasive carcinoma of the bladder (NMIBC) [2] and require long-term management and follow-up because of the risk of recurrence and progression.

For many years, urine cytology has been one of the cornerstones of the diagnosis and follow-up of patients with UCB [2]. Historical data established cytology to be highly specific, although sensitivity varies widely [3] and may be influenced by factors such as reader experience and history of bladder cancer [4]. The majority of data are relatively old, however, and concerns have been raised regarding the role and performance of cytology in contemporary practice [5].

Furthermore, advancements in optical equipment and the introduction of novel endoscopic techniques, such as narrow band imaging or blue-light cystoscopy (BLC) [6] may enhance bladder cancer visualization and detection rates. When only white-light cystoscopy (WLC) was available, it was not possible to truly assess when cytology was falsely negative. If WLC and cytology were both negative, then there was a natural assumption that there was no evidence of disease. Furthermore, tumour observed 3 months later was assumed to be a recurrence rather than a 'missed cancer'. The use of BLC showed, however, that WLC can miss > 20% of bladder tumours and 25–30% of carcinoma *in situ* (CIS) cases [6]. Since urologists still routinely use WLC and cytology for surveillance of bladder cancer, we sought to evaluate the performance of cytology based on contemporary data collected during prospective multi-institutional studies evaluating novel urinary markers or enhanced cystoscopy techniques.

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Our hypothesis was that, based on the enhanced performance of BLC, cytology performance may be even lower than historically reported.

Materials and Methods

Study Design

Individual, de-identified, patient data were obtained from the sponsors of three recently conducted prospective, multi-institutional trials: the Photocure (PC) B305 [7] (NCT00233402) and PC B308 [8] (NCT02560584) studies, evaluating the use of BLC with hexaminolevulinate (BLC-H) and the Cxbladder Monitor (CxbM) study [9] (NCT02700659), evaluating this urine marker for the detection of recurrent urothelial carcinoma (studies described below; Table 1). All studies included urine cytology as part of standard patient evaluation.

All studies were approved by our institutional review board, as needed, at the time of data collection. The requirement for informed consent for this *ad hoc* analysis was waived by the institutional review board.

Patients and Study Description

The PC B305 study [7] was a randomized phase III, prospective, multicentre study with the aim of comparing the performance of BLC-H and WLC in patients with suspected NMIBC on the basis of previously performed outpatient WLC, increased risk of recurrence (defined as > 1 tumour, recurrence within 12 months from prior resection, or recurrence with multiple tumours) and at least 3 months from last intravesical instillation. Individual patient data on all patients in the intention-to-treat groups of both arms (WLC and BLC-H), comprising a total of 547 patients, were obtained.

The PC B308 study [8] was a single-arm, phase III study, comparing BLC-H and WLC flexible cystoscopy for the detection of UCB in patients at high risk of recurrence, defined as history of multiple, recurrent or high grade NMIBC at least 6 weeks from last intravesical instillation. Individual patient data were obtained. Patients randomized to WLC, training set patients (first four patients in each centre), those who withdrew from the study and those with missing or unsatisfactory cytology specimens were excluded, resulting in 206 patients for the present analysis.

The CxbM [9] study was a single-arm multicentre prospective study evaluating the Cxbladder Monitor in patients undergoing surveillance for UCB recurrence. Patients were recruited from community and referral centres in the USA. Patients underwent investigative WLC (only), as part of standard follow-up. Patients were followed up for as many as three clinical visits, that is, each visit for which a cystoscopy was performed and urine cytology was collected; thus, each individual patient may be represented more than once. Data provided by the sponsor also included those from patients with primary suspected tumours not included in the final published data. After exclusion of patients/visits with no cytology data, our analysis included 734 samples collected from 622 individual patients.

Cytology and Pathology Correlation

All studies provided individual patient cytology and pathology data. In the PC B305 and PC B308 studies, cytology was evaluated locally, and pathology specimens were evaluated both locally and centrally. For the purpose of the present analysis, central pathology results were considered the 'gold standard'. In the CxbM study, cytology specimens were evaluated both by local pathologists and centrally, and pathological data were evaluated locally. Results are reported for both central and local cytology evaluation. When reporting pooled results, including data from all three studies, we included only those obtained by local cytology from the CxbM study as we believed this would better reflect common practice.

Cytology results for the purpose of the present analysis were considered negative if defined by the pathologists as negative or atypical, and positive if defined as suspicious or positive.

Table 1 Description of the included studies.

	Study		
	PC B305	PC B308	CxbM
Number of patients	547	206	622
Type of study	Randomized, phase III	Single-arm, phase III	Single-arm, phase III
Population	Suspected NMIBC based on previous WLC, high risk of recurrence	High risk of recurrence	Surveillance for UCB recurrence/primary tumours
Cystoscopy	WLC/BLC	WLC/BLC	WLC
Cytology analysis	Local	Local	Local + Central

BLC, blue-light cystoscopy; CxbM, Cxbladder Monitor; NMIBC, non-muscle-invasive carcinoma of the bladder; PC, Photocure; WLC, white-light cystoscopy.

Statistical Analysis

The specificity and sensitivity for each study and for the overall cohort were calculated; 95% CIs were calculated for pooled results. The chi-squared test was used to compare categorical variables when indicated. Statistical analysis was performed with SPSS statistics, version 25.0 (IBM, Armonk, NY, USA). Two-sided statistical significance was defined as $P < 0.05$.

Results

Cohort Characteristics

Our analysis included 1 487 urine samples from 1 375 patients, including 547 (36.8%), 206 (13.8%) and 734 (49.4%) samples from the PC B305, PC B308 and CxbM studies, respectively. Patient characteristics are shown in Table 2. Overall, there were 1 038 (75.5%) male and 337 (24.5%) female patients. All patients in the PC B308 study had a history of UCB, as defined by the inclusion criteria of this study, 476 of the patients in the CxbM (76.5%) had a history of UCB and 146 (23.5%) did not. Only the PC B308 study provided accurate information regarding previous tumours, and patients in this study included 172 (83.5%) with a history of high-grade disease and 97 (47%) with a history of CIS. In the PC B305 and B308 studies, 131 (23.9%) and 176 (85%) patients, respectively, had received prior BCG treatment.

Table 2 Cohort characteristics.

	Study					
	PC B305		PC B308		CxbM	
Number of patients	547		206		622	
Mean ± SD age, years	68.7 ± 10.5		69.2 ± 10.2		68.8 ± 11.9	
Gender, *n* (%)						
Male	436	(79.70)	159	(77.20)	443	(71.20)
Female	111	(20.30)	47	(22.80)	179	(28.80)
Race, *n* (%)						
White	NA		NA		536	(86.20)
Black	NA		NA		29	(4.70)
Other	NA		NA		57	(9.20)
Bladder cancer history, *n* (%)						
Yes	NA		206	(100)	476	(76.50)
No	NA		0	(0)	146	(23.50)
High grade history						
Yes	NA		172	(83.50)	NA	
No	NA		34	(16.50)	NA	
CIS history						
Yes	NA		97	47.10%	NA	
No/unknown	NA		109	52.90%	NA	
Prior BCG						
Yes	131	23.90%	176	85%	NA	
No	406	74.20%	30	15%	NA	

CxbM, Cxbladder Monitor; CIS, carcinoma in situ; NA, not available; NMIBC, non-muscle-invasive carcinoma of the bladder; PC, Photocure.

Cytology Performance

Overall, 615 tumours were diagnosed, correlating to 41% of the total cytology specimens collected. Of those, there were 70 low-grade/grade 1, 214 grade 2 and 331 high-grade/grade 3 tumours. A total of 106 tumours were CIS, 430 were Ta and 141 were T1 or above. In all, 313 cytology specimens (21%) were considered to be positive, while 1 174 samples (79%) were considered negative.

Cytology performance is summarized in Table 3. The sensitivity calculated for the overall population of each study was 44.8% for PC B305, 22.4% for PC B308, and 28.6% and 17.1% for CxbM locally and centrally evaluated cytology, respectively. The pooled sensitivity (including only local cytology from CxbM study results) was 40.8% (95% CI 35.9–46.1). The specificity was 85%, 84.5%, 95.5% and 92.9% for PC B305, PC B308 and CxbM locally and centrally evaluated cytology, respectively. The pooled cytology specificity for the overall cohort was 92.8% (95% CI 86.6–99.5).

The positive and negative likelihood ratios were 2.99/0.65, 1.45/0.92, 6.36/0.75 and 2.41/0.89 for PC B305, PC B308, CxbM locally and centrally evaluated cytology, respectively.

Stratified according to final pathological findings (Table 4), the pooled sensitivity was 57.5% (95% CI 44.0–73.9), 32.1% (95% CI 26.9–37.9) and 65.9% (95% CI 53.2–80.8) for CIS, Ta and ≥T1 disease, respectively. Stratified by grade, the pooled sensitivity was 11.4% (95% CI 5.9–22.5) for low-grade/WHO grade 1 disease and 54.3% (95% CI 46.7–62.9) for high-grade/WHO grade 3 disease. WHO grade 2 disease was only reported for PC B305, with sensitivity being 29.4%. Data from the CxbM study allowed comparison between local cytology performed in tertiary and community centres; sensitivity was 40% and 8%, respectively, and specificity 93.2% and 98.1%, respectively. The rate of cancer detection on cystoscopy was not significantly different based on centre type, with 11.3% for tertiary and 7.5% for community centres ($P = 0.08$).

Subgroup analysis based on prior BCG irrigations showed higher sensitivity of 46.9% (95% CI 41.7–52.1) in patients with no prior BCG irrigations compared with 30.7% in those who had received prior BCG irrigations (95% CI 23.8–38.3).

When stratified according to cystoscopy technique (data only available for the PC B305 and PC B308 studies), cytology sensitivities for WLC and BLC-H cases were 41.3% (95% CI 34.1–49.5) and 40.5% (95% CI 33.6–48.2), respectively. Specificity was 84.8% (95% CI 71.0–100) and 84.1% (95% CI 71.0–98.7), respectively. Subgroup analysis, including only patients with CIS from PC B305, showed a sensitivity of 54.5% (95% CI 32.3–86.2) for BLC-H and 69.2% (95% CI 45.6–100) for WLC.

Table 3 Cytology performance.

	Study				Overall	95% CI (if applicable)
	PC B305	PC B308	CxbM			
			Local	Central		
Number of specimens	547	206	734	734	1 487	
Overall						
Sensitivity, % (*n*/*N*)	44.80 (218/487)	22.40(13/58)	28.60(20/70)	17.10(12/70)	40.80	35.9–46.1
Specificity, % (*n*/*N*)	85.00(51/60)	84.50(125/148)	95.50(634/664)	92.90 (617/664)	92.80	86.6–99.5
PPV, % (*n*/*N*)	96 (218/227)	36.10 (13/36)	40 (20/50)	20.30 (12/59)	80.01	70.5–90.7
NPV, % (*n*/*N*)	15.90(51/320)	73.50(125/170)	92.70(634/684)	91.40(617/675)	68.99	64.3–73.9
Positive likelihood ratio	2.99	1.45	6.36	2.41	NA	
Negative likelihood ratio	0.65	0.92	0.75	0.89	NA	
History of UCB						
Sensitivity, % (*n*/*N*)	NA	22.40(13/58)	28.80(17/59)	13.60(8/59)	25.64	17.3–36.6
Specificity, % (*n*/*N*)	NA	84.50(125/148	94.70(501/529)	92.40(489/529)	92.47	85.3–100
No history of UCB						
Sensitivity, % (*n*/*N*)	NA	NA	27.30(3/11)	36.40(4/11)	NA	
Specificity, % (*n*/*N*)	NA	NA	98.50(133/135)	94.80(128/135)	NA	
Prior BCG						
Sensitivity, % (*n*/*N*)	33.10(40/121)	24.40(11/45)	NA	NA	30.72	23.8–38.3
Specificity, % (*n*/*N*)	100(10/10)	82.40(108/131)	NA	NA	83.68	76.5–89.4
No prior BCG						
Sensitivity, % (*n*/*N*)	48(172/358)	15(2/13)	NA	NA	46.90	41.7–52.1
Specificity, % (*n*/*N*)	81.30(39/48)	100.00(17/17)	NA	NA	86.15	75.3–93.5
White-light cystoscopy						
Sensitivity, % (*n*/*N*)	45.10(106/235)	22.90(11/48)	NA	NA	41.34	34.1–49.5
Specificity, % (*n*/*N*)	86.20(25/29)	84.50(109/129)	NA	NA	84.81	71.0–100
Blue-light cystoscopy						
Sensitivity, % (*n*/*N*)	44.40(112/252)	22.80(13/57)	NA	NA	40.45	33.6–48.2
Specificity, % (*n*/*N*)	83.90(26/31)	84.10(122/145)	NA	NA	84.09	71.0–98.7

CxbM, Cxbladder Monitor; PC, Photocure; PPV, positive predictive value; NPV, negative predictive value; UCB, urothelial carcinoma of bladder.

Discussion

As cytology is still being commonly used for the evaluation and follow-up of patients with UCB, we aimed to evaluate the performance of cytology based on contemporary data collected during three prospective, multicentre trials, specifically evaluating its performance when advanced cystoscopic techniques such as BLC-H were used. We found an overall sensitivity for cytology of 40.8%. The results varied when stratified according to final pathological stage, ranging from 32% for Ta tumours to 57% and 66% for CIS and ≥T1 tumours, respectively. When stratified by grade, cytology showed remarkably poor performance for low-grade tumours, with sensitivity of only 11.4%, pointing to the limited role of cytology in the follow-up of patients with low-grade disease, especially when classified as low-risk disease (i.e. solitary Ta tumour ≤3 cm) [10]. For high-grade tumours, sensitivity was higher at 54.3%, however, these results still suggest that > 40% of high-grade tumours and CIS lesions will be missed by cytology. Our results are similar to those reported by Yafi et al. [5] from a retrospective analysis of contemporary data from a single institution; they reported an overall sensitivity for cytology of 32%, ranging from 10% for low-grade tumours to 51% for high-grade tumours. Mowatt et al. [11] performed a meta-analysis and reported a pooled sensitivity of 44% for cytology, which was the lowest compared with other markers such as fluorescence in situ hybridization, ImmunoCyt and NMP22. Specificity was high at 96%, and positive and negative likelihood ratios were 10.8 and 0.58, respectively. Similarly, Lotan and Roehrborn [3] reported a median (range) overall sensitivity for cytology of 34 (20–53)%, which again was inferior to most other urine-based markers. The reported median (range) sensitivity for WHO grade 3 disease by Lotan and Roehrborn was 64 (38–84)%, with an overall specificity of 99 (83–99)%. Both meta-analyses mentioned above included some studies performed in the 1990s; however, our results, much like those reported by Yafi et al. [5], indicate that overall, along with the frequently quoted low sensitivity of cytology for the detection of low-grade disease, there has been no major improvement in the performance of cytology in recent years and detection of high-grade disease or CIS remains relatively low as well. With rates of progression of > 50% for untreated patients with CIS [12], the fact that cytology missed > 40% of tumours is concerning, especially considering these lesions are often also missed by cytoscopy. The use of cytology as the main

Table 4 Cytology performance by grade and stage.

	Study				Overall	95% CI (if applicable)
	PC B305	PC B308	CxbM			
			Local	Central		
Number of specimens	547	206	734	734	1 487	
Number of tumours detected, % (*n*)	89 (487)	28 (58)	9.5 (70)	9.5 (70)	615	
CIS*						
Sensitivity, % (*n*/*N*)	62.50 (45/72)	34.80 (8/23)	72.70 (8/11)	36.40 (4/11)	57.50	44.0–73.9
Ta						
Sensitivity, % (*n*/*N*)	34.90 (120/344)	18.90 (7/37)	22.40 (11/49)	10.20 (5/49)	32.10	26.9–37.9
≥T1						
Sensitivity, % (*n*/*N*)	73.20 (90/123)	22.20 (2/9)	11.10 (1/9)	33.30 (3/9)	65.90	53.2–80.8
Low grade (grade 1)						
Sensitivity, % (*n*/*N*)	27.30 (3/11)	4.30 (1/23)	11.10 (4/36)	8.30 (3/36)	11.40	5.9–22.5
Grade 2						
Sensitivity, % (*n*/*N*)	29.40 (63/214)	NA	NA	NA	NA	22.6–37.6
High grade (grade 3)						
Sensitivity, % (*n*/*N*)	58.00(152/262)	34.30(12/35)	47.10(16/34)	26.50(9/34)	54.30	46.7–62.9

*CIS, carcinoma in situ; CxbM, Cxbladder Monitor; PC, Photocure. *CIS was counted in separately from Ta\≥T1 stage hence total number of tumours per stage may exceed the number of tumours per grade.*

adjunct to cystoscopy in patients at high risk can lead to missed opportunities for early detection of recurrence and for determining which patients are not responding to intravesical therapies such as BCG.

Interestingly, the present results suggest better performance of cytology in patients with no BCG history compared with those who had received prior BCG, with sensitivity of 46.9% and 30.7%, respectively. A possible explanation for this finding may be related to difficulty in interpreting the cytological specimen after BCG irrigations. These results should be interpreted with caution, however, as exact data regarding patient disease history and timing of cytology after BCG irrigations were not available for analysis. Nevertheless, in line with our other results, this finding still points to the overall poor performance of cytology, especially in patients with a history of BCG treatment, who would most likely be considered to have at least intermediate-risk disease.

Notably, the present results suggest wide variability of the performance of cytology among the studies and between locally and centrally evaluated specimens, with relatively high sensitivity reported in the PC B305 study of 44% and the lowest sensitivity reported for centrally evaluated specimens in the CxbM study, at only 17%, which surprisingly performed worse than locally evaluated cytology, with a sensitivity of 28%. Wide variability between centres and interobserver variability has been previously reported [13]. Raitanen et al. [4] also observed a similar trend suggesting better performance by local pathologists, with 38.8% sensitivity compared to 31% by central review. When comparing community and tertiary centres, local cytology performed better in the latter, with sensitivity of 8% and 40%, respectively. While these differences may be influenced by the quality of cystoscopy, overall the rate of positive findings on cystoscopy was not significantly different between tertiary and community centres (11.3% and 7.5%, respectively).

The limitations of WLC have been recognized, and in fact, the AUA guidelines for NMIBC recommend the use of enhanced cystoscopy such as BLC-H at time of transurethral resection of bladder tumour to reduce the rates of missed tumours. A recent prospective trial found that flexible cystoscopy with blue light can detect additional tumours, including CIS [8]. Surprisingly, despite the expected higher detection rate of BLC-H, which could lower the sensitivity of cytology because more tumours are detected [6], comparison of the performance of cytology, when using WLC and BLC-H, showed similar sensitivities of 41.3% vs 40.4%, respectively. However, subgroup analysis for patients with CIS did suggest a lower sensitivity associated with BLC-H of only 54%. Several factors may explain these findings. First, all the patients in the PC B305 study had a suspicious lesion based on initial WLC and, of all the patients randomized to BLC-H in PC B305, only six presented with CIS lesions exclusively detected by BLC-H without any additional lesion detected by WLC. Secondly, many of the studies reporting on the superiority of BLC-H report this on a per-lesion basis [6], whereas, for the purpose of analysing the performance of cytology, we must consider per-patient analysis, so that cytology could be positive even if WLC did not identify all tumours. Flexible BLC-H, however, is now approved by the US Food and Drug Administration for use during surveillance of bladder cancer, and larger cohorts may very

well demonstrate decreased sensitivity of cytology in this setting.

The present study has several limitations. First, although based on prospectively collected data, this is an *ad hoc* analysis. Second, we acknowledge the significant differences in cohort characteristics and interventions across the studies included in the analysis and the possible risk of bias when pooling these results. Furthermore, missing data, especially regarding bladder cancer history, makes comparison even harder; however, this heterogeneous population may very well represent daily practice. It is also not clear how this should impact the cytopathologist who is reviewing the urine. A pathologist reviewing urine for patients with CIS in one clinical setting should be equally likely to detect abnormal cells in such patients in a different clinical setting. Third, cytology specimens were not collected in a uniform way across studies, which might have affected our results; however, these are real-world data and reflect practices at many centres. Fourth, only two of the studies reported on centrally evaluated pathology specimens and different grading systems were used. Fifth, each cytology specimen was correlated to the immediate cystoscopy performed after collection. We do not have adequate follow-up data on these patients, which might have influenced both specificity and sensitivity results. Finally, as the majority of patients in the present analysis had a history of bladder cancer, this may have implications for the applicability of our results to a population with haematuria.

Despite the fact that urine cytology is a commonly used adjunct to cystoscopy for UCB diagnosis and follow-up, there is considerable evidence that the sensitivity for detecting high-grade and CIS tumours remains low, as evident from our analysis of contemporary data. Further studies will be necessary to determine whether urine-based tumour markers can replace cytology. While they demonstrate superior sensitivity, there are still questions regarding the impact of specificity on clinical application [14,15]. Prospective studies incorporating urine markers into surveillance protocols may clarify their role [16]. The use of enhanced cystoscopy to improve detection of CIS and other high-grade tumours may also reduce the reliability of urologists with regard to cytology to avoid missing cancer recurrence.

In conclusion, based on analysis of contemporary data, the sensitivity of cytology for detecting high-grade and CIS tumours remains low. On a per-patient analysis, cytology sensitivity was not affected by the use of advanced cystoscopic techniques, although lower sensitivity was observed for CIS. The use of cytology as the main adjunct to cystoscopy in patients at high risk can lead to missed opportunities for the early detection of recurrence and for determining which patients are not responding to intravesical therapies, such as BCG.

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Conflict of Interest

Yair Lotan has received consultant fees from Photocure and Pacific edge.

References

1 **Siegel RL, Miller KD, Jemal A.** Cancer statistics, 2018. *CA Cancer J Clin* 2018; 68: 7–30

2 **Babjuk M, Oosterlinck W, Sylvester R et al.** EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. *Eur Urol* 2008; 54: 303–14

3 **Lotan Y, Roehrborn CG.** Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. *Urology* 2003; 61: 109–18

4 **Raitanen M-P, Aine R, Rintala E et al.** Differences between local and review urinary cytology in diagnosis of bladder cancer. An interobserver multicenter analysis. *Eur Urol* 2002; 41: 284–9

5 **Yafi FA, Brimo F, Auger M et al.** Is the performance of urinary cytology as high as reported historically? A contemporary analysis in the detection and surveillance of bladder cancer. *Urol Oncol* 2014; 32: 27.e1–e6

6 **Burger M, Grossman HB, Droller M et al.** Photodynamic diagnosis of non–muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. *Eur Urol* 2013; 64: 846–54

7 **Stenzl A, Burger M, Fradet Y et al.** Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. *J Urol* 2010; 184: 1907–14

8 **Daneshmand S, Patel S, Lotan Y et al.** Efficacy and safety of blue light flexible cystoscopy with hexaminolevulinate in the surveillance of bladder cancer: a phase III, comparative, multicenter study. *J Urol* 2018; 199: 1158–65

9 **Kavalieris L, O'Sullivan P, Frampton C et al.** Performance characteristics of a multigene urine biomarker test for monitoring for recurrent urothelial carcinoma in a multicenter study. *J Urol* 2017; 197: 1419–26

10 **Chang SS, Boorjian SA, Chou R et al.** Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. *J Urol* 2016; 196: 1021–9

11 **Mowatt G, Zhu S, Kilonzo M et al.** Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer. *Health Technol Assess* 2010; 14: 356

12 **Lamm D, Herr H, Jakse G et al.** Updated concepts and treatment of carcinoma in situ. *Urol Oncol* 1998; 4: 130–8

13 **Karakiewicz Pierre I, Benayoun S, Zippe C et al.** Institutional variability in the accuracy of urinary cytology for predicting recurrence of transitional cell carcinoma of the bladder. *BJU Int* 2006; 97: 997–1001

14 **Xylinas E, Kluth LA, Rieken M et al.** Urine markers for detection and surveillance of bladder cancer. *Urol Oncol* 2014; 32: 222–9

15 **Mbeutcha A, Lucca I, Mathieu R, Lotan Y, Shariat SF.** Current status of urinary biomarkers for detection and surveillance of bladder cancer. *Urol Clin North Am* 2016; 43: 47–62

16 **Clinton T, Lotan Y.** Review of the clinical approaches to the use of urine-based tumor markers in bladder cancer. *Rambam Maimonides Med J* 2017; 8: e0040

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Abbreviations: UCB, urothelial carcinoma of the bladder; NMIBC, non-muscle-invasive carcinoma of the bladder; BLC, blue-light cystoscopy; WLC, white-light cystoscopy; PC, Photocure; BLC-H, blue-light cystoscopy with hexaminolevulinate; CxbM, Cxbladder Monitor.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Investigator list for PC B305/308 and CxbM.

