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TOPIC PAPER

Impact of intravesical therapy for non-muscle invasive bladder cancer on the accuracy of urine cytology

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Abstract

Purpose Urine cytology remains an essential diagnostic tool in the surveillance of patients with non-muscle invasive bladder cancer (NMIBC). The correlation of urine cytology with biopsy specimens to determine its accuracy following induction intravesical therapy has not been investigated.

Methods A retrospective review was performed of patients who underwent intravesical therapy for biopsy-proven non-muscle invasive disease between 2013 and 2016 at our institution. All patients uniformly underwent cytology and systematic bladder biopsies in the operating room within 12 weeks following intravesical therapy. The accuracy of urinary cytology in predicting high-grade disease recurrence following intravesical therapy was confirmed by correlating cytology results to post-treatment systematic biopsies, regardless of endoscopic findings. Only patients with complete information regarding urine cytology and pathologic biopsy results, both pre- and post-intravesical therapy, were included.

Results 90 cytology samples following intravesical therapy were analyzed from 76 patients who met inclusion criteria. 72 (80.0%) and 18 (20.0%) of the samples were collected from patients initially treated for high- and low-grade disease, respectively. Fifty-six (62.2%) specimens were obtained from patients following induction of bacillus Calmette–Guerin (BCG) therapy; the remainder were from patients treated with intravesical gemcitabine/docetaxel, mitomycin, or BCG/interferon. For patients treated with BCG, cytology was positive for high-grade disease in 8/15 patients with high-grade pathology on follow-up biopsy, thus demonstrating a sensitivity of 53% (95% CI 27–79%), specificity of 95% (95% CI 84–99%), positive predictive value of 80% (95% CI 44–98%), and negative predictive value of 85% (95% CI 71–94%). If cytologic interpretation was broadened to include high-grade and "suspicious for high-grade" findings, sensitivity increased to 67% (95% CI 38–88%) and specificity decreased to 88% (95% CI 74–96%).

Conclusions While urinary cytology maintains a high specificity following intravesical therapy, it demonstrates a low sensitivity for potentially aggressive high-grade urothelial carcinoma. Further evaluation of more effective, clinic-based enhanced cystoscopy techniques and biomarkers is warranted to better identify patients at risk for disease recurrence following BCG therapy.

Keywords Urinary bladder neoplasms · Urine cytology · Urothelial carcinoma · Bacillus Calmette–Guerin

Introduction

Contemporary evidence has found that as many as 70–80% of patients with non-muscle invasive bladder cancer (NMIBC) will have cancer recurrence after the initial treatment, and nearly 20% will progress to muscle-invasive disease within 5 years [1–5]. Thus, while patients with NMIBC have favorable survival outcomes, the risk of cancer recurrence and progression to muscle-invasive disease necessitate timely and extended surveillance strategies. Surveillance protocols for NMIBC have historically relied on the

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diagnostic combination of cystoscopy and urinary cytology, which has been reported to have high specificity (> 90%) for high-grade (HG) lesions, including carcinoma in situ (CIS) [2, 6]. As a result, a positive cytology reading, regardless of cystoscopic or radiographic findings, is concerning for the presence of malignancy in the majority of patients [7].

Urinary cytology, however, has several drawbacks. Cytologic evaluation can be hampered by low cellular yield and inflammation secondary to infection, stones, or intravesical instillations [3]. Additionally, urinary cytology is not a laboratory test—it is based upon a pathologist's interpretation of the morphologic features of exfoliated urothelial cells [2]. Cytologic interpretations are often consequently associated with interobserver variability and a wide range of readings (e.g., atypical, atypical suspicious, non-diagnostic) [3]. As a result, the accuracy of cytology is dependent on the level of expertise of the pathologist [6].

Despite the recognition that significant inflammation immediately following intravesical instillations can impede cytologic evaluation, urinary cytology remains a cornerstone in the surveillance of patients with NMIBC who receive intravesical therapy for CIS, HG T1, or high-risk Ta urothelial carcinoma. There is limited data, however, on the effect of intravesical therapy on the sensitivity and specificity of cytology in detecting disease recurrence [8, 9]. We present an analysis in which all patients uniformly underwent systematic biopsies following intravesical therapy, regardless of endoscopic findings, and correlated their pathology to urinary cytology. This is the first study to our knowledge to provide pathologic confirmation in all patients with high-risk NMIBC following intravesical treatment to determine the accuracy of cytology.

Materials and methods

Patient population and study design

A retrospective review was performed of an IRB-approved institutional database of patients with biopsy-proven NMIBC managed with induction intravesical therapy, including both treatment-naïve patients and those undergoing repeat induction therapy, between 2013 and 2016. Patients who completed bacillus Calmette–Guerin (BCG) therapy underwent at least five instillations, and all patients included began intravesical therapy within 6 weeks of restaging transurethral resection. After completing intravesical therapy, all patients uniformly underwent urinary cytology and standardized bladder biopsies in the operating room, regardless of cystoscopic findings. Biopsies were performed utilizing white light cystoscopy within 12 weeks following intravesical treatment [median = 6.9 weeks (5.1–11.3 weeks)]. Patients with negative endoscopic findings underwent random biopsies of the bladder and prostatic urethra. Patients who did not adequately complete induction therapy and those without complete information regarding urinary cytology and biopsy results, both pre- and post-intravesical therapy, were excluded. Patients in whom completion of induction BCG required more than 7 weeks or who underwent biopsy after 12 weeks were also excluded. Upper tract imaging was performed as a component of the initial evaluation of all patients, during surveillance of all patients at 1–2 year intervals, and in patients with persistently positive cytology following intravesical therapy. All biopsy and cytology results were evaluated by genitourinary pathologists and cytopathologists at our institution.

Data collection, analysis, and outcomes

Biopsy results were evaluated for evidence of disease recurrence and progression following intravesical therapy, and outcomes were stratified according to initial biopsy stage and type of intravesical therapy administered. Biopsy results were staged according to TNM criteria, and grade was assessed using the 1998 WHO tumor grading system [10–12]. Cytology specimens were graded using the Johns Hopkins Template from 2013 to July 2016 and the Paris System for Reporting Urinary Cytology after August 2016 (Table 1) [13–15]. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of urinary cytology in predicting HG disease recurrence following intravesical induction was confirmed by post-intravesical therapy biopsies. Data analysis was performed using Stata, Version 13 (StataCorp LP, College Station, TX).

Results

Study population and patient characteristics

A total of 90 cytology samples were analyzed from 76 patients who met the inclusion criteria; 14 of the 76 patients underwent repeat induction therapy for BCG-unresponsive disease and consequently had multiple cytologies. Baseline

Table 1 Categories for pathological descriptions of urinary cytology

Cytology categories
Unsatisfactory/non-diagnostic
Negative for high-grade urothelial carcinoma
Atypical urothelial cells (of uncertain significance)
Low-grade urothelial neoplasm/urothelial carcinoma low-grade
Suspicious for high-grade urothelial carcinoma/cannot exclude high-grade urothelial carcinoma
High-grade urothelial carcinoma

demographic and pathologic (pre-intravesical therapy) characteristics are outlined in Table 2. 72 (80.0%) and 18 (20.0%) of the samples were collected from patients initially treated for high- and low-grade disease, respectively. Fifty-six (62.2%) specimens were obtained from patients following induction of BCG therapy; the remainder were from 20 patients treated with second-line intravesical gemcitabine/docetaxel ($n=18$, 20.0%), mitomycin ($n=10$, 11.1.9%), or BCG/interferon ($n=6$, 6.7%) secondary to BCG-unresponsive disease. Second-line therapies were utilized in patients that had previously failed BCG therapy.

Disease recurrence and progression

For all patients managed with BCG, a total of 15/56 patients (26.8%) were noted to have BCG-unresponsive HG disease on their post-treatment biopsy: 4/15 (26.7%) had Ta disease, 7/15 (46.7%) had T1 disease, 5/15 (33.3%) had CIS with papillary tumors, and 4/15 (26.7%) were found to have CIS only on pathology (Table 3). No patients were noted to have disease progression to muscle-invasive disease on initial post-BCG biopsy. Forty-one (73.2%) patients demonstrated a complete response, defined as having negative biopsies and a negative cytology (Table 4).

Fourteen patients (25.0%) in the cohort elected to undergo radical cystectomy due to BCG-unresponsive disease at a median of 4.3 months following completion of the final intravesical therapy (Table 4). Of this subset, three patients were found to have T3 disease on final pathology; the cystectomies were performed at 3.2, 10.5, and 17.5 months following intravesical therapy. The patient who underwent cystectomy at 3.2 months was found on initial follow-up to have high-grade urothelial carcinoma on cytology with a benign biopsy, while the other two patients had benign biopsies and cytologies at first follow-up. The three patients subsequently recurred with high-grade disease on biopsies at later dates, however, and therefore elected to proceed to radical cystoprostatectomy. The remaining 11 patients who underwent radical cystoprostatectomies were found to have NMIBC in their surgical cystoprostatectomy specimens.

Accuracy of urinary cytology

For all patients treated with induction BCG, cytology was positive for HG disease in 8/15 patients with HG pathology on follow-up biopsy. Cytology demonstrated a sensitivity of 53% (95% CI 27–79%), specificity of 95% (95% CI 84–99%), PPV of 80% (95% CI 44–98%), and NPV of 85% (95% CI 71–94%) (Table 5, Figs. 1, 2). If cytologic interpretation was broadened to include HG and "suspicious for HG" findings, the sensitivity of cytology increased to 67% (95% CI 38–88%) and specificity

Table 2 Patient demographics and baseline pathological characteristics

	Total	BCG	Other intravesical therapies
N	90	56 (62.2%)	34 (38%)
Age (year)	69.9 (54.9–84.5)	70.0 (59.0–81.0)	69.6 (60.1–79.1)
Gender			
Male	76 (84%)	46 (82%)	30 (88%)
Female	14 (16%)	10 (18%)	4 (12%)
Race			
White	77 (86%)	48 (86%)	29 (85%)
Black	4 (4%)	1 (2%)	3(9%)
Other	9 (10%)	7 (13%)	2 (6%)
Smoking history			
Never smoked	27 (30%)	15 (27%)	12 (35%)
Current/former smoker	63 (70%)	41 (73%)	22 (65%)
Initial TURBT grade (pre-therapy)			
LG	18 (20%)	7 (13%)	11 (32%)
HG	72 (80%)	49 (88%)	23 (68%)
Initial TURBT grade (pre-therapy)			
Ta (pure)	41 (46%)	22 (39%)	19 (56%)
T1 (pure)	14 (16%)	11 (20%)	3 (9%)
CIS (pure)	20 (22%)	11 (20%)	9 (26%)
Ta + CIS	7 (8%)	5 (9%)	2 (6%)
T1 + CIS	8 (9%)	7 (13%)	1 (3%)

Data are presented as n (%) or median (interquartile range)

LG low-grade, *HG* high-grade, *BCG* bacillus Calmette–Guerin, *CIS* carcinoma in situ

Table 3 Characteristics of patients with BCG-refractory HG disease following intravesical BCG induction therapy

Patient	Age	Gender	Initial TURBT pathology	Post-BCG biopsy pathology	Post-BCG cytology
1	75.5	Male	Hg T1 + CIS	Hg T1 + CIS	AUC
2	67.1	Male	Hg Ta	CIS	AUC
3	69.7	Female	Hg T1 + CIS	Hg Ta	Suspicious for HGUC
4	73.0	Male	CIS	CIS	HGUC
5	72.8	Female	Hg Ta	Hg Ta	NHGUC
6	81.9	Male	Hg Ta + CIS	CIS	AUC
7	87.0	Male	Hg Ta	Hg T1	HGUC
8	83.6	Male	Hg Ta	Hg Ta	HGUC
9	84.0	Male	Hg Ta	CIS	Suspicious for HGUC
10	59.3	Female	Hg Ta	Lg Ta + CIS	NHGUC
11	75.5	Male	Hg T1	Hg T1	HGUC
12	80.7	Male	Hg T1 + CIS	Hg T1 + CIS	HGUC
13	81.3	Male	Hg T1 + CIS	Hg T1 + CIS	HGUC
14	55.7	Male	Hg T1	Hg T1	HGUC
15	67.7	Male	Hg T1 + CIS	Hg T1 + CIS	HGUC

HG high-grade, *LG* low-grade, *TURBT* transurethral resection bladder tumor, *BCG* bacillus Calmette–Guerin, *CIS* carcinoma in situ, *HGUC* high-grade urothelial carcinoma, *NHGUC* negative for high-grade urothelial carcinoma, *AUC* atypical urothelial cells (of uncertain significance)

Table 4 Biopsy and cytology characteristics of eventual cystectomy patients

Patient	Last therapy received	Initial pathology	Post-therapy biopsy pathology	Post-therapy cytology	Months to cystectomy	Cystectomy grade	Node status
1	BCG	HgT1	Benign	HGUC	3.2	T3	0/37
2	BCG	HgTa	HgTa	NHGUC	3.4	CIS	0/13
3	GEM/DOCE	HgTa	CIS	NHGUC	3.5	CIS	0/14
4	BCG + IFN	CIS	CIS	AUC	3.8	Benign	0/24
5	BCG	HgTa	CIS	AUC	3.9	Benign	0/3
6	BCG + IFN	CIS	CIS	AUC	4.1	HgTa + CIS	0/21
7	BCG	HgTa	HgTa	SHGUC	4.2	T1	0/29
8	BCG	HgTa	CIS	SHGUC	4.4	T1	0/52
9	BCG	CIS	Benign	SHGUC	7.8	CIS	0/7
10	GEM/DOCE	HgTa + CIS	Benign	AUC	10.0	CIS	0/11
11	BCG	CIS	Benign	NHGUC	10.5	T3	2/23
12	BCG	HgTa	Benign	SHGUC	11.8	CIS	0/31
13	BCG	HgTa	Benign	NHGUC	17.5	T3	0/32
14	GEM/DOCE	HgTa	Benign	AUC	21.2	CIS	0/57

HG high-grade, *LG* low-grade, *BCG* bacillus Calmette–Guerin, *GEM/DOCE* gemcitabine/docetaxel, *IFN* interferon, *CIS* carcinoma in situ, *HGUC* high-grade urothelial carcinoma, *NHGUC* negative for high-grade urothelial carcinoma, *AUC* atypical urothelial cells (of uncertain significance), *SHGUC* suspicious for high-grade urothelial carcinoma/cannot exclude high-grade urothelial carcinoma

decreased to 88% (95% CI 74–96%) (Fig. 3, Table 5). All patients treated with BCG for intermediate-risk NMIBC were found to have benign cytology and biopsies (seven patients).

Urinary cytology maintained a relatively low sensitivity of 52% (95% CI 31–73%) and high specificity of 96% (95% CI 88–99%) in patients treated with any intravesical therapy, including BCG.

Discussion

Urinary cytology has historically been reported to demonstrate a high specificity for high-grade urothelial carcinoma (> 90%), including CIS [2, 6, 16]. Urinary cytology has not, however, previously been correlated with mandated post-treatment bladder biopsies to determine if

Table 5 Accuracy of urinary cytology following intravesical therapy stratified by cytology definition in patients with HG pathology on post-therapy TURBT

Definition of "Positive Cytology"	Initial TURBT pathology	Intravesical therapy	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Definitive HG	HG + LG	BCG	53% (27–79)	95% (84–99)	80% (44–98)	85% (71–94)
Definitive HG	HG	BCG	53% (27–79)	94% (80–99)	80% (44–98)	82% (67–93)
Definitive HG + suspicious for HG	HG + LG	BCG	67% (38–88)	88% (74–96)	67% (38–88)	88% (74–96)
Definitive HG	HG + LG	All	52% (31–73)	96% (88–99)	80% (52–96)	85% (75–92)

HG high-grade, *LG* low-grade, *PPV* positive predictive value, *NPV* negative predictive value, *BCG* bacillus Calmette–Guerin

	D	ND	
+	8	2	10
-	7	39	46
	15	41	56

Fig. 1 Definitive HG cytology versus HG pathology after BCG. *D* HG pathology (disease), *ND* no HG pathology (no disease), (+) positive cytology, (−) negative cytology

	D	ND	
+	8	2	10
-	7	32	39
	15	34	49

Fig. 2 Definitive HG cytology versus HG pathology after BCG in patients with initial HG pathology only. *D* HG pathology (disease), *ND* no HG pathology (no disease), (+) positive cytology, (−) negative cytology

it maintains this level of diagnostic accuracy following intravesical therapy. To evaluate the effect of intravesical therapy on the accuracy of urinary cytology in detecting HG disease, we utilized histology from systematic post-treatment bladder biopsies, obtained regardless of cystoscopic findings, and compared it to urinary cytology in a consecutive series of patients treated with BCG and other second-line therapies for NMIBC. In comparing biopsy results and cytology interpretations, we found that

	D	ND	
+	10	5	15
-	5	36	41
	15	41	56

Fig. 3 Definitive + suspicious HG cytology versus HG pathology after BCG. *D* HG pathology (disease), *ND* no HG pathology (no disease), (+) positive cytology, (−) negative cytology

urinary cytology maintained a high specificity of ≥ 95% for HG disease following induction of both BCG and other intravesical therapies. This is an important finding as most urologists depend on cytology to supplement endoscopic and radiologic evaluation of the urinary tract to detect clinically significant HG urothelial carcinoma. Patients with these lesions have the potential for recurrence, progression, and metastases; they represent a high-risk population that would ideally undergo surveillance with a biomarker that demonstrates both high sensitivity and high specificity for HG disease to reliably identify recurrence early. Because it maintains a high specificity even in the post-BCG setting, as our study demonstrates, urologists can feel confident that further evaluation should be pursued in the setting of a patient treated for NMIBC with a positive surveillance cytology, and that the cytology interpretation is not necessarily a false positive secondary to an inflammatory state following intravesical therapy.

Although cytology has historically been reported to have a high sensitivity for detecting HG lesions (up to 84%), contemporary series do not support this notion. Cytology has been demonstrated a sensitivity ranging between 34 and 60% for HG lesions in recent studies [17–22]. These findings are further emphasized by a multicenter study by Grossman et al. [17] in 2005 involving over 1300 patients

at an elevated risk for bladder cancer that found that cytology had an overall sensitivity of 15.8% and a sensitivity of 37.5% for patients with high-grade tumors. It is unclear why the reported sensitivity rates have declined in literature and may be secondary to a lack of consensus in cytology interpretation, variations in cytology collection methods, and differences in patient pre-test probabilities. In a post-BCG induction setting in patients treated for NMIBC, cytology demonstrated a sensitivity of 53% (95% CI 27–79%) in our study. When cytologic interpretation was broadened to include HG and "suspicious for HG" findings, the sensitivity of cytology increased to 67% (95% CI 38–88%). Thus, in both the pre- and post-BCG settings, cytology offers low sensitivity for high-grade tumors, including CIS. A positive voided urinary cytology consequently can indicate the presence of a malignant lesion in the urinary tract (given the high specificity of cytology); a negative cytology does not, however, rule out the presence of a tumor [2, 23].

There have been several recent efforts to address shortcomings in the use of urine cytology. The Paris System for Reporting Urine Cytology (TPS) has recently emerged as a significant international and multi-institutional collaboration to help standardize urine cytology reporting and to further focus the application of cytology towards the detection primarily of HG urothelial carcinoma by minimizing atypical diagnoses [13]. The requirement of additional cytological features such as hyperchromasia, irregular nuclear membranes, or clumpy chromatin pattern to define a cell as atypical, for example, has resulted in fewer cases being assigned to the anomalous interpretation and has helped shift cytologies with minimal atypia towards the non-high-grade urothelial carcinoma category [24]. By standardizing cytologic features for each category, TPS has helped minimize the number of diagnoses being placed in the atypical category, thus focusing urologists' awareness to specimens with severe atypia concerning for high-grade disease. Cowan et al. [25] showed that when applied to urinary cytology specimens of patients with pathologically proven high-grade bladder cancer, TPS criteria improved specimen risk stratification by upgrading approximately 40% of indeterminate specimens into higher-risk categories. Furthermore, by excluding atypia related to low-grade (LG) urothelial neoplasms and reactive conditions such as infections or intravesical therapy away from the atypical category, urologists can use cytology more effectively to separate patients with high-risk lesions from those with LG urothelial carcinoma, most of whom have a low risk of progression.

In recent years, there has also been an increased interest in the development of urine-based biomarkers as potential diagnostic alternatives or as adjuncts to cytology and cystoscopy [26]. Several of these markers have been approved by the FDA and are commercially available in the US [27]. While many urine markers exhibit promising sensitivity, particularly for lower-grade tumors, their specificity has largely been found to be lower than that of urine cytology [2, 3]. Many of these markers also remain to be tested in the post-intravesical therapy setting, where reliable identification of disease recurrence is essential in patients with high-risk NMIBC. Furthermore, lack of prospective data to support the impact of urinary biomarkers on patient prognosis has limited their widespread adoption at this time. As a result, until a more effective urinary marker is developed for detecting potentially lethal urothelial carcinoma, especially following intravesical therapy, urine cytology will likely continue to serve as a cornerstone for surveillance for NMIBC. Nevertheless, future investigations of other urinary markers are indicated for the surveillance of patients with NMIBC, and especially in the post-BCG setting, where early identification of patients at risk for disease recurrence and progression is essential.

Enhanced cystoscopy techniques have also emerged and have demonstrated their ability in improving the detection of malignant tumors, particularly CIS, compared to conventional white light cystoscopy (WLC) [3, 28–30]. Studies have found that using blue light cystoscopy (BLC), for example, both small papillary lesions and almost one-third more cases of CIS that are overlooked by WLC can be identified [2, 28, 31, 32]. A phase III trial of 146 patients with known or suspected bladder tumors found that 96% of all tumors were detected with BLC compared with 77% using standard WLC [33]. BLC has also been shown to decrease the risk of bladder cancer recurrence. A meta-analysis based on raw data of prospective trials reported a significant increase in detection of malignant lesions in BLC arms and an absolute reduction of 10% in recurrence rates within 1 year (35% versus 45%; RR 0.761; $p = 0.006$) [29]. Notably, however, researchers have found higher false positive results for BLC compared to WLC, particularly in patients who have recently undergone TURBT, who have concurrent UTI/inflammation, or who have recently received intravesical BCG or chemotherapy [3]. Thus, while the use of enhanced cystoscopy has been shown to improve the detection of malignant tumors, data on its use in the surveillance setting is limited. The reported false positive rates of BLC decrease over time with experience [34], however, and additional studies are underway evaluating the use of enhanced cystoscopy techniques for surveillance purposes. In the interval, guidelines still advise the use of urinary cytology to supplement cystoscopic evaluation [3, 23].

There are limitations of our study. First, we utilized a relatively small cohort size. The patients included, however, all uniformly underwent systematic bladder biopsies after undergoing intravesical therapy, thus providing histologic confirmation of post-treatment cytology specimens. Second, as a tertiary care center, a significant number of our patients are referred to our institution for management after

diagnosis, and pre-treatment urinary cytology was often unavailable for review from patients' initial assessments. While evaluation of the accuracy of urine cytology preceding intravesical therapy would have allowed us to demonstrate an internal control, the sensitivity and specificity of cytology are well-documented in the literature.

Conclusions

Our study suggests urinary cytology maintains a high specificity for HG urothelial tumors following intravesical therapy compared to established rates in the literature and can be used to identify patients at risk for disease recurrence and progression. Until the development of a urinary biomarker that demonstrates improved specificity for aggressive NMIBC emerges, cytology will likely remain an essential part of surveillance strategies. Further evaluation of more effective, clinic-based enhanced cystoscopy techniques and biomarkers is warranted to better identify patients at risk for disease recurrence following BCG therapy.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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