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ORIGINAL ARTICLE

Prognostic value of urinary cytology and other biomarkers for recurrence and progression in bladder cancer: a prospective study

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Abstract
Purpose Urinary cytology (C) and cystoscopy remain the gold standard for the detection and screening of bladder cancer (BC). In this prospective study, we analyzed whether baseline C, ImmunoCyt (I), BTA *Stat* (B), hemoglobin dipstick (H), and NMP22 BladderChek (N) can predict recurrence and progression.
Methods Urinary samples from 91 patients with BC were prospectively collected over an 18-month period. Baseline characteristics of the population included patient demographics, various clinicopathological variables and use of intravesical therapy. Progression and recurrence were then assessed after a median follow-up of 48 months (IQR 23.7–59.5). Univariate and multivariate analyses were performed using COX proportional hazards models.
Results On univariate analysis, C (HR 1.36; $p = 0.26$), I (HR 0.89; $p = 0.66$), B (HR 0.80; $p = 0.42$), H (HR 0.75; $p = 0.30$), and N (HR 0.82; $p = 0.48$) were not associated with recurrence-free survival (RFS). With regard to progression-free survival (PFS), C was significantly prognostic (HR 2.67; $p = 0.017$), whereas I, B, H, and N were not. On multivariable analysis, NMP22 was the only marker to be independently associated with RFS (HR 0.41, $p < 0.01$) and PFS (HR 0.32, $p = 0.02$).
Conclusion Based on the results of this study, baseline C, B, I, and H were not independently prognostic. Prognostic impact of NMP22 requires further validation in a multicenter larger study.

Keywords Bladder cancer · Urinary biomarkers · Urinary cytology · Recurrence · Progression

Introduction

In North America, bladder cancer (BC) is the sixth most common cancer [1, 2]. The majority are non-muscle-invasive bladder cancer (NMIBC) at the time of diagnosis, confined to the mucosa (stage Ta, CIS) or the submucosa (stage T1) [3]. Although these tumors have a good prognosis, 30–70 % will have a recurrence and 10–30 % will progress to more aggressive disease [4–6]. The progression of this disease greatly increases the risk of metastasis and the associated morbidity and mortality.

The gold standard treatment of NMIBC remains transurethral resection ± intravesical therapy followed by routine and long-term surveillance with cystoscopy and urinary cytology (C) [7–9]. The requirement for frequent invasive testing has resulted in BC having the highest cumulative cost per patient from diagnosis to death of any cancer [10]. Urine cytology has a high specificity; however, its poor sensitivity especially for low-grade tumors requires the continued use of cystoscopy in follow-up. The ability of cytology to detect occult CIS preserves its role within detection and surveillance for bladder cancer [11].

ImmunoCyt, BTA *Stat*, hemoglobin dipstick, and NMP22 BladderChek are four commercially available non-invasive urine tests that have been studied with improved sensitivity over urine cytology [12–14]. ImmunoCyt (I) is a microscopic test that incorporates fluorescent-labeled antibodies that target 3 markers of malignant urothelial cells.

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BTA *Stat* (B) detects the presence of complement factor H-related protein produced by malignant cells. It is a variant of complement factor H which protects normal cells from the complement system. Hemoglobin dipstick (H) is used to detect blood in the urine. NMP22 BladderChek (N) detects nuclear matrix protein 22 in the urine, a protein that provides structural support for the nucleus and ensures separation of genetic material during mitosis. To date, none of the four urinary biomarkers have yielded results that allow providers to replace cystoscopy in the detection of BC [15]. Although all the above-mentioned markers were studied to assess the sensitivity and specificity to detect bladder cancer, none of them have been evaluated with regard to their prognostic role. In this prospective study, we set out to analyze whether baseline urine cytology and other noninvasive urinary markers can predict bladder cancer recurrence and progression.

Materials and methods

As previously described [16], between July 2007 and January 2009 urinary samples were collected from 109 consecutive patients enrolled in a single center clinical trial following IRB approval. Patients with a suspicious lesion on cystoscopy were eligible. Those who had <3 months (and/or lost to) follow-up were excluded. This resulted in a group of 91 patients. Baseline urinary samples were analyzed for cytology, hemoglobin dipstick, BTA Stat, NMP22 BladderChek, and ImmunoCyt at time of TURBT. These markers were selected based on the inclusion of all the known urinary biomarkers that our institution had access to. Patient demographics, date of urinary sample collection, type of specimen (voided, washing, or catheterized), and surgical pathology were collected. In August 2014, charts were reviewed for last follow-up date and disease status.

All voided urine cytology samples were prepared as ThinPrep slides, while other samples (washing and catheterized) were prepared as cytospin or as a smear preparation after centrifugation. All were subsequently stained with the Papanicolaou stain. All were reviewed by one of four academic pathologists with training in cytopathology. As previously reported, only carcinoma or those that were suspicious for carcinoma were considered clinically positive [17]. On the same day of cystoscopy, all biomarkers were prepared according to the instructions provided with the commercially available kits. Histological specimens were graded according to the 2004 World Health Organization grading system [18].

Univariable and multivariable analyses by using Cox proportional hazards models were performed with recurrence and progression as endpoints. Variables with a p value <0.25 on univariable analysis were included in multivariate analysis for the same endpoints, using cytology and each marker independently and separately as forced variables. Follow-up started at the initial time of urinary marker testing and the end date set as the date of last follow-up or death. Accordingly, each marker was modeled as a time-fixed binary variable. A p value <0.05 was considered statistically significant. All analyses were performed using the SAS version 9.1.3 Service Pack four statistical (window platform).

Results

Study population

A total of 91 patients had sufficient data for inclusion in the study. The median follow-up period was 48 months with an interquartile range of 23.7–59.5 months and a mean of 44.5 months. There were 54 (61 %) patients with at least one recurrence, and 26 (29 %) patients experienced progression of their disease during the follow-up period. The clinical and pathological characteristics of the patients are given in Table 1. The number of patients with positive C, I, B, H, and N was 41 (45 %), 48 (53 %), 45 (49 %), 45 (49 %), and 43 (47 %), respectively. The number of patients with malignancy confirmed on histology at the time of the TURBT was 84 (92 %). Intravesical therapy (BCG ± interferon alpha) was used in 39 (43 %) patients.

Prognostic impact of urinary markers

Univariable analysis: Using COX regression analysis, cytology (HR 2.67, $p = 0.017$) and stage (HR 2.67, $p = 0.02$) were significantly associated with disease progression (Table 2). No other urinary marker was associated with recurrence-free survival (RFS) or progression-free survival (PFS).

Multivariable analysis: On multivariable analysis, NMP22 was the only marker to be independently associated with RFS (HR 0.41, $p < 0.01$) and PFS (HR 0.32, $p = 0.02$) (Table 3). Stage and lymphovascular invasion were associated with progression (Table 4). Urine cytology was no longer associated with PFS on multivariate analysis (HR 1.41, $p = 0.48$). Similarly, B, H, and I were not associated with RFS or PFS.

Discussion

In this prospective study, NMP22 was independently prognostic for disease recurrence and progression. Urine cytology, Immunocyt, BTA stat, and hemoglobin dipstick did not demonstrate any prognostic impact.

Table 1 Baseline patient, clinical, and pathological characteristics of 91 consecutive patients

Age, median years (range)	74 (45–96)
Race	
Caucasian	76 (84 %)
Other	15 (16 %)
Gender	
Male	76 (84 %)
Female	15 (16 %)
BMI, median (range)	26 (17–34)
Smoker	
Positive	81 (89 %)
Negative	10 (11 %)
Reason for collection	
First presentation	34 (37 %)
Surveillance	57 (63 %)
Type of specimen	
Voided	69 (76 %)
Other	22 (24 %)
Urine analysis	
Negative for RBC	14 (21 %)
Positive for RBC	51 (79 %)
Histology	
Malignant	84 (93 %)
Benign	7 (7 %)
Grade	
Low	40 (47 %)
High	44 (53 %)
Tumor type	
UC	77 (92 %)
Mixed	6 (7 %)
Non-UC	1 (1 %)
Pathology	
<T1	56 (62 %)
T1	15 (16 %)
T2	20 (22 %)
Architecture	
Sessile	7 (8 %)
Papillary	77 (92 %)
Number of tumors, median (range)	1 (1–12)
Recurrence	
Yes	54 (61 %)
No	35 (39 %)
Progression	
Yes	26 (29 %)
No	63 (71 %)

Table 2 Univariate analysis of recurrence and progression using COX regression

	Recurrence HR (95 % CI); *p*	Progression HR (95 % CI); *p*
Cytology	1.37 (0.79–2.4); 0.26	2.67 (1.19–6.01); 0.02
ImmunoCyt	0.89 (0.52–1.51); 0.66	0.96 (0.44–2.08); 0.92
BTA *stat*	0.80 (0.46-1.38); 0.42	1.38 (0.63–3.01); 0.42
Hemastix	0.75 (0.44–1.29); 0.30	1.04 (0.48–2.25); 0.92
NMP22	0.82 (0.48–1.41); 0.48	0.89 (0.41–1.93); 0.77
Intravesical therapy[a]	1.67 (0.97–2.85); 0.06	0.95 (0.44–2.06); 0.90
Smoker	1.70 (0.68–4.27); 0.26	0.80 (0.28–2.32); 0.68
Stage	1.85 (0.94–3.62); 0.07	2.67 (1.15–6.18); 0.02
Grade	1.51 (0.87–2.64); 0.15	1.99 (0.90–4.43); 0.09
Multifocality	1.60 (0.84–3.06); 0.15	1.19 (0.48–2.98); 0.70
CIS	1.31 (0.52–3.30); 0.57	2.51 (0.81–7.32); 0.09
Gender	0.94 (0.47–1.88); 0.86	1.70 (0.71–4.06); 0.23
LVI	1.22 (0.61–2.43); 0.57	2.11 (0.88–5.03); 0.09

NMIBC non-muscle-invasive bladder cancer, *MIBC* muscle-invasive bladder cancer, *CIS* carcinoma in situ, *LVI* lymphovascular invasion

[a] Intravesical therapy defined as minimum of 6-week induction therapy with BCG ± interferon alpha

Presently, the standard of care for a newly detected papillary tumor is transurethral resection ± intravesical therapy followed by surveillance with interval cystoscopy and urine cytology. We sought to identify whether the baseline status of commercially available urinary markers can predict recurrence and progression of disease to help counsel patients and tailor frequency of invasive monitoring. The study population was representative of the published literature with respect to stage, rate of recurrence, and rate of progression of disease [3, 4, 6]. Examining different multivariate analyses while forcing each individual urine marker separately demonstrated that the only marker that was significantly associated with RFS and PFS was NMP22. However, and paradoxically, a positive NMP22 was associated with decreased RFS and PFS.

NMP22 has been identified as a marker for recurrence and/or progression in different patient populations. In previous studies, the marker analysis was performed post-TURBT [19], at the time of cystectomy [20], or following negative cystoscopy [21]. Our study differed in that tumor markers were tested at the time of first cystoscopy for suspected bladder masses and followed for future episodes of recurrence or progression post-resection. It has also been shown that after controlling for age and gender, the absolute value of NMP22 correlated with the likelihood of diagnosing tumors by cystoscopy [22]. Although I, H, C, and B did not predict RFS or PFS in our population, there did appear to be a protective effect from N. This improved survival can in part be explained by the false-positive rates associated with overnight fasting, hematuria, and recent urinary tract instrumentation [23–26]. Furthermore, studies have shown an increase in the ability of N to detect low-grade disease compared with urine cytology [27]. The

Table 3 Multivariate analysis of recurrence using COX regression

Variable	Cytology HR (95 % CI); *p*	ImmunoCyt HR (95 % CI); *p*	BTA *stat* HR (95 % CI); *p*	Hemastix HR (95 % CI); *p*	NMP22 HR (95 % CI); *p*
Urine marker	0.98 (0.52–1.85); 0.96	0.65 (0.37–1.16); 0.14	0.54 (0.27–1.08); 0.08	0.60 (0.34–1.07); 0.08	0.41 (0.21–0.80); 0.01
Intravesical therapy	1.91 (1.03–3.55); 0.04	1.84 (0.99–3.42); 0.05	1.71 (0.92–3.18); 0.09	1.81 (0.98—3.36); 0.06	1.93 (1.06–3.52); 0.03
Stage NMIBC versus MIBC	1.78 (0.78–4.05); 0.17	1.95 (0.86–4.39); 0.11	2.07 (0.91–4.70); 0.08	1.87 (0.86–4.08); 0.12	1.91 (0.88–4.16); 0.10
Grade Low versus high	1.09 (0.55–2.17); 0.80	1.14 (0.58–2.23); 0.71	1.43 (0.69–2.99); 0.34	1.18 (0.61–2.29); 0.62	1.73 (0.83–3.59); 0.14
Multifocality	1.65 (0.84–3.22); 0.14	1.63 (0.83–3.17); 0.15	1.41 (0.71–2.81); 0.33	1.57 (0.81–3.06); 0.18	1.59 (0.80–3.14); 0.18

NMIBC non-muscle-invasive bladder cancer, *MIBC* muscle-invasive bladder cancer

Table 4 Multivariate analysis of progression using COX regression

Variable	Cytology HR (95 % CI); *p*	ImmunoCyt HR (95 % CI); *p*	BTA *stat* HR (95 % CI); *p*	Hemastix HR (95 % CI); *p*	NMP22 HR (95 % CI); *p*
Urine marker	1.41 (0.54–3.70); 0.48	0.44 (0.17–1.14); 0.09	0.67 (0.25-1.79); 0.42	0.76 (0.34–1.71); 0.51	0.32 (0.12–0.86); 0.02
Intravesical therapy	0.59 (0.23–1.54); 0.28	0.57 (0.22–1.49); 0.25	0.57 (0.21–1.49); 0.25	0.62 (0.24–1.59); 0.31	0.64 (0.26–1.55); 0.32
Stage NMIBC versus MIBC	1.01 (0.35–2.94); 0.98	1.29 (0.45–3.71); 0.63	1.21 (0.42–3.52); 0.72	1.17 (0.41–3.32); 0.76	1.13 (0.41–3.09); 0.82
Grade Low versus high	2.58 (0.84–7.89); 0.10	2.93 (1.00–8.61); 0.05	3.17 (1.04–9.68); 0.04	2.85 (0.97–8.38); 0.06	4.96 (1.53–16.02); 0.01
CIS	1.64 (0.52–5.19); 0.40	2.57 (0.78–8.42); 0.12	2.15 (0.67–6.93); 0.20	1.96 (0.64–5.96); 0.24	2.85 (0.87–9.28); 0.08
Gender	1.66 (0.64–4.28); 0.294	1.76 (0.69–4.48); 0.23	1.71 (0.67–4.34); 0.26	1.82 (0.72–4.65); 0.21	1.88 (0.71–5.02); 0.21
LVI	2.31 (0.84–6.38); 0.11	3.24 (1.17–9.01); 0.02	2.67 (0.97–7.33); 0.06	2.37 (0.87–6.40); 0.09	3.51 (1.21–10.22); 0.02

NMIBC non-muscle-invasive bladder cancer, *MIBC* muscle-invasive bladder cancer, *CIS* carcinoma in situ, *LVI* lymphovascular invasion

assay detects nuclear mitotic apparatus protein 1, with experimental models questioning whether it truly detects malignant cells or simply cell turnover [24]. Other studies have shown specific cytokine panels can predict response to BCG therapy [28]. Whether N can also be portrayed as a surrogate marker of inflammation that predicts response to intravesical therapy requires further evaluation.

The use of intravesical therapy in our study demonstrated a decreased RFS, although there existed an inherent selection bias as only those deemed to be high risk of recurrence would have received the treatment. Finally, FISH has previously been shown to predict future recurrence and progression [29]. At the initial time of our study, FISH could not be included at our institution as part of the analysis since it was not available in Canada, precluding the validation of its ability to predict RFS and PFS.

Small sample size is the main limitation of this study. Furthermore, using consecutive patients provided a population with a mixture of new diagnoses and recurrences that were tested as index cases. Although this introduced some heterogeneity into the population, it is clinically representative of current urologic practices. The strength of this study is the prospective design testing multiple markers within the same population and an adequate follow-up.

Conclusion

Urine cytology, Immunocyt, BTA stat, and hemoglobin dipstick do not predict recurrence or progression of bladder cancer. Baseline NMP22 status was significantly prognostic for disease relapse. Further larger multicenter validation is warranted to confirm these findings.

Authors' contribution M.D. Bell was involved in data collection and data analysis and wrote the manuscript. F.A. Yafi, F. Brimo, J. Steinberg, A.G. Aprikian, and S. Tanguay were involved in data collection. W. Kassouf was involved in project development and data collection and edited the manuscript.

Compliance with ethical standards

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

Informed consent This study met the ethical standards of our internal review board, and informed consent was obtained from all patients prior to inclusion.

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