ELSEVIER

Urologic Oncology: Seminars and Original Investigations 32 (2014) 27.e1–27.e6

UROLOGIC ONCOLOGY

Original article

Is the performance of urinary cytology as high as reported historically? A contemporary analysis in the detection and surveillance of bladder cancer

Faysal A. Yafi[a,1], Fadi Brimo[b,1], Manon Auger[b], Armen Aprikian[a], Simon Tanguay[a], Wassim Kassouf[a,*]

[a] *Department of Surgery, McGill University Health Center, Montreal, Quebec, Canada*
[b] *Department of Pathology, McGill University Health Center, Montreal, Quebec, Canada*

Received 3 August 2012; received in revised form 22 September 2012; accepted 22 September 2012

Abstract

Objectives: The goal of this study was to evaluate sensitivity and specificity of urine cytology during a contemporary period at our institution in comparison with historical analysis and other reported urinary biomarkers.

Materials and methods: Data from 1,114 consecutive patients corresponding to 3,251 specimens (2,979 cytologic and 272 histologic specimens) between January 2006 and July 2006 were retrieved. Subsequent cytologic and surgical specimen reports were examined with a minimum 2-year follow-up period. Collected parameters included the date of collection, reason for urinary evaluation, type of specimen, and tumor grade. Atypical diagnosis was considered negative.

Results: On cytologic examination, 71% of specimens were benign, 23% atypical, and 6% suspicious or positive for urothelial carcinoma. Reason for collection was surveillance in 61% and new symptoms in 28%. Depending on the tumor grade, sensitivity results ranged from 10% for low-grade to 51% for high-grade tumors. Importantly, specificity of urine cytology ranged from 83% to 88% (depending on the type of urine collection and type of clinical presentation). Anticipatory positive rate was 44% after a median time of 15 months. Specificity of other reported urinary markers ranges from 40% to 90%.

Conclusion: Our institution's experience with regard to specificity of urine cytology is lower than reported historically. Whether this is a consequence of heterogeneous study designs and parameters is open to debate. As the anticipatory positive rate was high, close surveillance remains recommended in patients with positive urine cytology and negative workup. Other institutions are encouraged to evaluate whether there remains a significant advantage for urine cytology over other urinary marker assays within their own clinical setting.

Keywords: Urine cytology; Bladder cancer; Cancer detection; Cancer surveillance; Urinary biomarkers; Sensitivity; Specificity

1. Introduction

Urothelial carcinoma of the bladder (BC) is the eighth most common cancer in the USA [1]. Approximately 75% to 85% of patients with BC present with disease confined to the mucosa or submucosa [2]. However, these tumors recur in 30% to 70% of the patients and in 10% to 30% progress to high-grade or invasive disease or both, thus worsening the prognosis of the patients [3–5]. Estimates show that 1 in every 1,450 people in the Western world is currently under surveillance for bladder cancer by cystoscopy and urine cytology [6]. On a per patient basis from diagnosis to death, bladder cancer is the most expensive to treat [7]. Importance of early detection of new tumors and the optimization of surveillance of already existing ones cannot be overstated.

Urinary cytology is the direct microscopic investigation of shed urothelial cells. As it was first described in 1945, it has continued to be used for the detection of neoplastic cells in the urine [8]. Although it is a convenient noninvasive test with historically high specificity for BC (in excess of 95%), it has poor sensitivity especially for low-grade tumors; as such, a negative result cannot exclude the presence of a low-grade disease [2]. Further drawbacks include the fact that its interpretation can be difficult in patients with inflammation, it is operator dependent, and its accuracy is affected by cellular yield [9,10].

* Corresponding author. Tel.: +1-514-934-8246; fax: +1-514-934-8297.
E-mail address: wassim.kassouf@muhc.mcgill.ca (W. Kassouf).
[1] FY and FB have equal first authorship.

1078-1439/$ – see front matter
http://dx.doi.org/10.1016/j.urolonc.2012.09.011

Visualization +/− histologic review of tissue by way of cystoscopy remains the mainstay for the detection and surveillance of BC. As such, it is currently the gold standard against which other detection and surveillance techniques should be gauged. However, as with cytology, cystoscopy has its limitations as it is perceived as an invasive procedure; though highly sensitive, can be inconclusive at times secondary to grossly abnormal appearance of the bladder mucosa; and may also fail to identify smaller, flat tumors such as carcinoma in situ (CIS) [2].

Because of the low sensitivity of urine cytology, the invasive nature of cystoscopy, and the cost associated with surveying these tumors, efforts have been put forth to find urinary biomarkers that would be noninvasive, simple, efficient, and objective and have high sensitivity and specificity. Although data so far have not justified replacing urine cytology with other markers primarily because of the very high specificity of urine cytology in historical reports, they have shown improved sensitivity over urine cytology, especially in low-grade tumors, suggesting they could play a role alongside cystoscopy in the future with the surveillance of known bladder tumors [11].

In this article, we aimed to evaluate the sensitivity and specificity of urine cytology during a contemporary period at our institution and compare it with historical analysis in an attempt to further assess the continued role of urinary cytology in the detection and surveillance of BC.

2. Materials and methods

Retrospective data from the institution's pathology registry were collected for all reviewed urine cytologic specimens between January 1 and July 1, 2006. Relevant patient medical records were subsequently accessed, and all cytologic and histologic specimens dating up to June 2008 were collected with a minimum 2-year follow-up. Clinical and pathologic variables that were examined included the date of collection, reason for urinary evaluation (first presentation of hematuria, surveillance for known hematuria or urothelial tumors, and others), type of specimen (voided, washing, or catheterized), and tumor stage/grade according to the 2004 World Health Organization grading system [12].

In order to most accurately reflect real-life practice, cytologic specimens were not reviewed after the initial reading. All voided urine cytology samples were prepared as ThinPrep slides, whereas other samples (washings 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 the 4 academic pathologists with training in cytopathology.

Cytologic specimens were divided into 4 main categories: benign that included reactive urothelial cells and instrumentation effects; atypical; suspicious for carcinoma; and urothelial carcinoma. The cytologic criteria used for an atypical diagnosis were the same used in prior studies from our institution [13]. Cytologic diagnoses were then subgrouped into 2 major clinical diagnoses: negative and positive. Any atypical specimen was considered as a negative diagnosis. Specimens that were suspicious for carcinoma were labeled as clinically positive.

Similarly, histologic specimens were not reviewed after they had been initially read by academic pathologists with genitourinary tract expertise. They were also divided into categories according to the World Health Organization classification [12]: benign, urothelial papilloma, papillary neoplasm of low malignant potential (PUNLMP), low-grade urothelial carcinoma (LGUCA), high-grade urothelial carcinoma (HGUCA), and CIS. Subsequently, they were coded as histologically positive if they were LGUCA, HGUCA, or CIS and as histologically negative if they were benign or papilloma. CIS was included in the HGUCA category. Because PUNLMP is a clinically borderline lesion that cannot be detected in cytologic specimens, it was excluded from the analysis.

To calculate sensitivity and specificity of urine cytology, correlation was made between urinary cytologic and histologic specimens. As is the case in clinical practice, histology obtained from cystoscopy samples with biopsies was considered as the "true" reflection of diagnosis. To avoid the correlation of different cytologic and histologic specimens, which may have included new tumors not previously present, we opted to follow the arbitrary period of 1 year between cytologic and histologic specimens. This time interval has been previously used in the literature as well as in prior reports emanating from our institution [13,14].

Accordingly, 3 different cytology-histology correlation models can be implemented. In the first model, for each patient, every single cytologic specimen is compared with a histologic specimen performed within 1 year. In the second one, each patient's histology is correlated with only 1 cytology. As such, when the histology is positive, if there is any positive cytology within the accepted time frame, it is used for the correlation and is considered a true positive. Otherwise, a negative cytology is used and is considered a false negative. When the histology is negative, if there is any prior positive cytology, it is used for correlation and considered a false positive. If all cytologies are negative, then it is a true negative. Finally, in the third model, with each patient, only 1 histologic specimen is looked at and is correlated with the clinically closest cytologic specimen within a 1-year period. When a positive histologic specimen is found, it is always used. If it is preceded by any positive cytology, this was considered a true positive. When there are no preceding positive cytologies, then it is labeled as a false negative. When all patient histologies are negative, if there are any preceding positive cytologies, they are used and the correlation is considered a false positive. Finally, when all cytologies are negative, this is considered a true negative.

Although all methods of correlation are valid, we opted to use the third method, which we felt was the most