EUROPEAN UROLOGY ONCOLOGY XXX (2018) XXX–XXX

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

Collaborative Review – Bladder Cancer

Optimal Trial Design for Studying Urinary Markers in Bladder Cancer: A Collaborative Review

Yair Lotan [a,*], *Peter C. Black* [b], *Laura Caba* [c], *Sam S. Chang* [d], *Michael S. Cookson* [e], *Siamak Daneshmand* [f], *Ashish M. Kamat* [g], *James M. McKiernan* [h], *Raj S. Pruthi* [i], *Chad R. Ritch* [j], *Gary D. Steinberg* [k], *Robert S. Svatek* [l], *Ellen C. Zwarthoff* [m]

[a] *Department of Urology, UT Southwestern Medical Center, Dallas, TX, USA;* [b] *Vancouver Prostate Centre, University of British Columbia, Vancouver, BC, Canada;* [c] *MDxHealth Inc., Irvine, CA, USA;* [d] *Vanderbilt University Medical Center, Nashville, TN, USA;* [e] *Department of Urology, The University of Oklahoma Health Sciences Center and The Stephenson Cancer Center, Oklahoma City, OK, USA;* [f] *USC Institute of Urology, USC Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA;* [g] *MD Anderson Cancer Center, Houston, TX, USA;* [h] *Department of Urology, Columbia University Irving Medical Center, New York, NY, USA;* [i] *Department of Urology, University of North Carolina at Chapel Hill, and Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA;* [j] *Department of Urology, University of Miami Leonard M. Miller School of Medicine, Miami, FL, USA;* [k] *Department of Surgery, Section of Urology, The University of Chicago, Chicago, IL, USA;* [l] *Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA;* [m] *Department of Pathology, Erasmus MC, Rotterdam, The Netherlands*

Article info

Article history:
Accepted April 17, 2018

Associate Editor:
Paul Nguyen

Keywords:
Bladder cancer
Urinary markers
Detection
Surveillance

Abstract

Context: Urine-based tumor markers are not routinely used in the diagnosis and surveillance of bladder cancer. The main limitation of urinary markers has been a lack of clarity regarding clinical benefit.

Objective: To review the indications for urinary marker use, barriers to marker utilization, and clinical trial designs for markers available for detection (hematuria populations) and surveillance (bladder cancer populations). The study aim was to facilitate an optimal trial design that could change clinical practice.

Evidence acquisition: A PubMed search was conducted on February 17, 2018, using the MeSH search terms "Urinary Bladder Neoplasms" [Mesh] AND "Biomarkers" [Mesh] AND "Urine" [Mesh] yielded 127 articles, of which only two also fulfilled the search term "Randomized Controlled Trial" [Publication Type]. Neither of these two articles examined clinical outcomes for patients but rather focused on the performance characteristics of the urinary marker. For the search terms "Hematuria" [Mesh] AND "Randomized Controlled Trial" [Publication Type] AND "Urinary Bladder Neoplasms" [Mesh] yielded 12 articles, none of which used randomization with the outcome of interest being a clinical endpoint.

Evidence synthesis: Several potential designs for urinary marker trials were developed for detection and surveillance of bladder cancer. A marker-based approach compared to usual care for evaluation of hematuria in a primary care setting could reduce unnecessary cystoscopy in patients with low risk and expedite care in patients with higher risk. For bladder cancer surveillance, marker-based approaches could reduce cystoscopy for patients with low-grade disease and potentially improve detection for patients with high risk.

Conclusions: Urinary markers are not currently routinely used owing to the absence of level 1 evidence supporting incorporation of urinary markers into protocols for detection or surveillance of bladder cancer. This review provides practical designs for studies that could demonstrate superiority of marker-based approaches over current clinical care. The sample sizes required for these studies are no greater than many of those accrued for previous urinary marker studies, but the proposed trial concepts require planning and a willingness to risk failure of the marker to demonstrate the desired benefits.

Patient summary: In this review we discuss current limitations in the use of urinary markers for detection and surveillance of bladder cancer. We identify potential studies that could demonstrate a clinical benefit of the use of markers in improving detection of bladder cancer by reducing evaluation of patients unlikely to have cancer or expediting identification of cancer. For surveillance, a marker trial could improve identification of bladder cancer or reduce cystoscopy in patients with low risk.

* Corresponding author. Department of Urology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9110, USA. Tel.: +1 214 6480483; Fax: +1 214 6488786.
E-mail address: yair.lotan@utsouthwestern.edu (Y. Lotan).

https://doi.org/10.1016/j.euo.2018.04.010
2588-9311/

Please cite this article in press as: Lotan Y, et al. Optimal Trial Design for Studying Urinary Markers in Bladder Cancer: A Collaborative Review. Eur Urol Oncol (2018), https://doi.org/10.1016/j.euo.2018.04.010

1. Introduction

Urothelial carcinoma of the bladder (UCB) ranks as the ninth most frequently-diagnosed cancer worldwide, with the highest incidence rates observed among men in Southern and Western Europe, North America, and certain countries in Northern Africa and Western Asia [1]. Approximately 25% of newly diagnosed bladder cancers are muscle-invasive or metastatic [2]. The majority of cancers are currently diagnosed via detection of blood in the urine; however, screening for bladder cancer is not advised [3]. For noninvasive disease managed by transurethral resection and intravesical therapies, there is a high risk of disease recurrence and variable risk of disease progression. Therefore, surveillance with repeat endoscopic evaluation is warranted following initial tumor removal [4].

Current detection and surveillance of bladder cancer are based on cystoscopic evaluation and urologist-dependent use of urine cytology or other urinary markers. Many urine-based tumor markers have been developed that are based on differential expression of proteins, cellular antigens, DNA, or RNA in the urine of patients harboring tumors compared to control patients without tumor. Currently, none of these markers is recommended by guideline panels for routine use, and their utilization is infrequent but variable [3,5]. Many urinary markers have superior sensitivity to cytology, especially for low-grade cancers. However, the specificity and consequently the positive predictive value (PPV) of most urinary markers is inferior to cytology. This is detrimental to clinical utilization because such markers often contribute to unnecessary procedures and anxiety [6].

There are a variety of reasons why urinary markers have not been widely accepted into clinical practice, including performance characteristics (sensitivity and specificity), cost, ease of use, and availability, but perhaps the main issue is lack of clarity regarding the clinical benefit [7]. Here we review the indications for urinary marker use, barriers to marker utilization, and the clinical trial designs available for markers for detection (hematuria populations) and surveillance (bladder cancer populations). The goal of this work is to facilitate an optimal trial design that could change clinical practice.

2. Evidence acquisition

To improve care through the use of biomarkers, it is important to develop trials that test clinical benefit. Our PubMed search conducted on February 17, 2018, using the MeSH search terms “Urinary Bladder Neoplasms” [Mesh] AND “Biomarkers” [Mesh] AND “Urine” [Mesh] yielded 127 articles, of which only two also met the search term “Randomized Controlled Trial” [Publication Type]. Neither of these two articles examined clinical outcomes for patients, but rather focused on the performance characteristics of a urinary marker. The search terms “Hematuria” [Mesh] AND “Randomized Controlled Trial” [Publication Type] AND “Urinary Bladder Neoplasms” [Mesh] yielded 12 articles, none of which used randomization with the outcome of interest being a clinical endpoint. To date, urine-based marker studies for UCB detection or surveillance address marker performance with no trials testing the ability of markers to improve clinical outcome.

3. Evidence synthesis

3.1. Indications for marker use

There are several potential indications for the use of urinary markers in the diagnosis and management of UCB. Most patients are diagnosed after finding either microscopic or gross hematuria and only rarely via an incidental finding on imaging [8]. Screening for UCB is not recommended owing to its low incidence in the general population and relatively low incidence even in high-risk populations [9]. The prevalence of microscopic hematuria ($\geq$3 red blood cells per high-power field) in the adult population is as high as 10–14% but the likelihood of finding UCB during evaluation of microscopic hematuria is low, even in patients with higher risk [10–12]. Urinary markers could improve risk stratification of patients with hematuria with the goal of expediting care of patients with a high risk of urothelial malignancy and potentially avoiding cystoscopy in patients with very low risk [13–15]. Another area of potential use is in improving the performance of cystoscopy. A urologist who is aware that the patient has a positive urinary marker might examine the bladder more carefully or use enhanced cystoscopy because of the higher likelihood that cancer might be present [16].

Surveillance is an area with significant potential for incorporation of a urinary marker. Since the risk of recurrence and progression varies according to tumor characteristics, the role of a urinary marker varies depending on whether the disease is of low, intermediate, or high risk [3,5]. In patients with low risk, the goal for a urinary marker may be to avoid or delay cystoscopy, while for patients with high risk a marker may serve to identify disease missed by cystoscopy. There are other scenarios in which a potential benefit of marker use has been demonstrated, such as in patients with atypical cytology or cystoscopy results [3,17]. Similarly, a marker that can predict response to therapy such as intravesical bacillus Calmette-Guérin could facilitate early identification of patients who should change management or enter clinical trials [18].

3.2. Barriers to current utilization

There are a variety of barriers to utilization of urinary markers, mostly related to a lack of studies demonstrating a clinical benefit over standard care. Many studies have demonstrated superior sensitivity of urinary markers over cytology, which is the urinary marker most commonly used; however, their specificity is lower than that of cytology [6,7,19]. The consequence of low specificity is that the PPV of most urinary markers ranges from 10% to 20%. Therefore, most urologists do not want to change their management basis on a positive urinary marker. This contrasts with the

Please cite this article in press as: Lotan Y, et al. Optimal Trial Design for Studying Urinary Markers in Bladder Cancer: A Collaborative Review. Eur Urol Oncol (2018), https://doi.org/10.1016/j.euo.2018.04.010