Old and New Urinary Markers: Which One is the PSA for Bladder Cancer?

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Abstract

Objectives: To review the role of urinary-based markers in the management of bladder cancer.

Methods: A literature search was performed to examine the field of urinary-based markers for bladder cancer. The principles for an ideal test to detect bladder cancer using a urinary assay were defined. Reported biomarkers were evaluated for their potential to fulfil these principles.

Results: Many of the criteria defined by Wilson and Junger for a screening program can be applied to urinary-based bladder cancer markers. Biomarkers can be used to either diagnose the disease or survey patients to detect progression or recurrence following initial endoscopic surgery. These roles are separate and different biomarkers may be needed to reflect the biology of these processes. To date, NMP22 appears as one of the best evaluated biomarkers, but its role needs to be clearly defined. Most biomarkers detect one form of bladder cancer, either invasive or noninvasive, and thus have a lower sensitivity than needed to replace cystoscopy.

Conclusions: Many reported urinary-based biomarkers can be used within appropriate management regimens to reduce cystoscopic burden and produce economic savings. No biomarker reported to date is sufficiently accurate to replace the need for cystoscopy.

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1. The need for a urinary assay

Bladder cancer (BCa) is a common malignancy and the prognosis of the disease is proportional to the stage at treatment [1]. Detection of the disease at an early stage improves the prognosis for the minority of tumours with the invasive phenotype [2]. Consequently, most health care systems have rapid-access flexible cystoscopy programs for patients with symptoms suggestive of BCa, and endoscopic treatment regimens include frequent cystoscopical surveillance to detect recurrent or progressive disease [3]. Thus, BCa is one of the most expensive malignancies in the Western world. It was estimated in 2001 the cost of BCa from diagnosis to death was between $96,000 and $187,000/patient [4].

Noninvasive methods to detect BCa that are safe, easy, and reliable would undoubtedly reduce the
morbidity, mortality, and economics of the disease. With respect to outcome, the application of such methods would enable more frequent surveillance or even population screening and, if accurate enough, would avoid the problems of cystoscopic surveillance, such as false-positive/negative examinations (e.g., in the presence of denuded cystitis or bacillus Calmette-Guérin [BCG] cystitis) and under-staging. Reports have shown that the prognosis for muscle-invasive tumours may be worse for those that progress under surveillance than for those that are invasive at presentation [5]. Economically, the main expense for BCa surveillance, the requirement of trained surgical expertise to perform the cystoscopy, would be avoided by the use of a urinary assay. Estimates using NMP22 suggest that urinary biomarkers when used with less frequency or replacing cystoscopy can save around 18% of surveillance costs [6] or $82–326 per new cancer diagnosed [7].

2. The application of a urinary assay

The criteria defined by Wilson and Junger for assessing the performance of a screening program appear suitable to use when discussing the role of a urinary-based assay for BCa [8]. These criteria can be divided into those related to the population involved, the disease being studied, the test used, and the health economic consequences of screening.

2.1. The population involved

It must first be stated that population screening for BCa, even with a noninvasive urinary-based test, is unlikely to be cost effective or to produce significant reductions in mortality. At least two well-described population screening programs have been reported and in both the overall incidence of BCa was 1.2–1.3% [2,9–11]. Of these few cases, around 45% were high grade and half of these already had muscle invasion. Thus, the capacity to improve outcomes using screening in the general population is low, given the few patients with early invasive tumours. However, populations at high risk of BCa can be defined because many etiologic risk factors are known. For example, cigarette smoking increases the risk of BCa 4-fold and occupational exposure to chemical carcinogens may account for 20% (or more) of all tumours [12]. Targeting high-risk populations with BCa screening could produce significant reductions in mortality at a frequency to justify the expense.

The majority of use for a urinary assay for BCa would be in surveillance for patients previously diagnosed with the disease. These patients are compliant (because they are anxious about their disease state) and would welcome the replacement of invasive cystoscopic examination.

2.2. The disease: BCa

For a screening or surveillance test to be beneficial it must identify the disease at a stage where treatment significantly improves the prognosis. A urinary-based assay that can diagnose BCa whilst confined to the urothelium or carcinoma in situ could fulfil this criterion. However, the majority of bladder tumours belong to the noninvasive phenotype. For these tumours early diagnosis, before the onset of symptoms, is unlikely to alter overall survival rates, even if it does reduce recurrence rates and morbidity (by treating lower-volume cancers). It is mainly tumours of the invasive pathway (around 25–33% of all BCa) that would benefit from early diagnosis and treatment. In these cancers a clear relationship exists between stage at diagnosis and outcome [1,13] in a patient presenting with symptoms. Although evidence suggests this relationship persists in a screened [2] population, studies suggest it may not hold true in surveyed patients [5].

2.3. The urinary assay

It seems likely that a urinary-based assay should be able to accurately detect the presence of BCa. The disease is in contact with urine constantly, malignant cells are shed into the urine, and it is likely that urine contains the carcinogens producing the malignancy. However, the concept that a single molecular marker can detect all BCa accurately is probably false given our understanding of the molecular biology of this cancer [14]. Clinical and molecular data support each other and suggest that tumours of the noninvasive and invasive BCa pathways are different [15,16]. The former pathway is indolent in terms of invasion and characterised by FGFR3 mutation, loss of part of chromosome 9, and a few other events [17,18]. Tests that aim to detect noninvasive tumours should be targeted toward these molecular events and be used to detect recurrence of superficial disease [19,20]. Tests that aim to detect noninvasive tumours should be targeted toward these molecular events and be used to detect recurrence of superficial disease [19,20]. The invasive pathway is characterised by numerous molecular events including p53 mutation, high levels of chromosomal instability, resulting in chromosome amplification or deletion, and widespread changes in DNA methylation [15,21–23]. Molecular assays for these tumours should target these events and are likely to be different from those needed to detect noninvasive tumours.
An extensive review of urinary assays for bladder cancer is beyond the scope of this article. The reader is referred to one of the many excellent recent reviews in this field, such as the recent international consensus panel statement [24]. As summarised in Table 1, assays have been developed against abnormal urinary proteins (such as complement factor-H, NMP-22, BLCA-1, BLCA-4, survivin, and various cytokeratins) or the presence of malignant cells within the urine (microsatellite analysis, telomerase, DNA methylation, or fluorescence in situ hybridisation). The majority of these markers have similar performance characteristics in that they can identify high-grade disease but fail to reliably detect low-grade tumours. As such their sensitivities, specificities, and accuracies are moderate (60–80%; Table 1) and insufficient to replace cystoscopy. Few markers have been evaluated as far as phase 3 multi-institutional studies, with NMP22 being one example [25,26]. Recent reports of a point-of-care assay reveal that NMP22 has diagnostic and surveillance sensitivities of 55.7% and 49.5%, respectively. Importantly, the combined use of NMP22 and cystoscopy improved the diagnosis of recurrent tumours, including high-grade superficial disease. The limited number of assays that have been evaluated into phase 3 studies is disappointing and reveals the inherent hurdles and costs [27,28].

2.4. Health economic implications

Several authors have modeled the effect of introducing a urinary biomarker for BCa analysis and surveillance. Most agree that cost savings of around 20% could be made by the reduction in cystoscopic surveillance frequency or the avoidance of diagnostic cystoscopy [6,7,29]. These projections use markers with 60–70% sensitivities and higher specificities. More savings could be made by better performing markers.

3. The next prostate-specific antigen

When urinary markers are evaluated for BCa, a comparison with prostate-specific antigen (PSA) is often made. One should remember that this assay has a poor specificity and sensitivity (as highlighted in the Prostate Cancer Prevention Trial [30]). Thus, the aim in BCa should be to better the target set by PSA and reduce patient morbidity, rather than increasing the intervention (prostate biopsy rate or cystoscopy) rate.

Conflicts of interest

The author has nothing to disclose.

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