URINARY BLADDER CANCER

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Bladder cancer is the second most common genitourinary malignancy. The American Cancer Society estimated that 61,420 new cases of bladder cancer would be diagnosed in the United States during 2006 and about 13,060 individuals would die of the disease.(1)

Many patients with bladder cancer experience recurrence but do not die of the disease. While bladder cancer is only the fourth most common cancer in men after lung, colorectal and prostate cancers, in terms of incidence it is the second most prevalent malignancy in middle-aged and elderly men after prostate cancer.(2),(3)

The current standard of care for detecting and monitoring bladder tumors is cystoscopy, voided urine cytology and imaging.(4)

However, cystoscopy is invasive, painful and costly. Therefore, it is not suitable as a screening test. Although urine cytology is a noninvasive test, it is limited by its low sensitivity of 20% to 40% for low grade tumors. Several methods have been reported for the early detection of bladder cancer using various potential markers. (5– 8)

The specificity and sensitivity of these tests vary between 50% and 100%. Therefore, they are not adequate for screening patients. Ideally a urine based bladder tumor marker would be noninvasive, inexpensive and nonuser dependent, and have high accuracy. Optimal markers would serve for screening, initial diagnosis, and monitoring recurrence and progression as well as predicting prognosis.

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 bladder cancer (BCa) [9].

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.

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% [10, 11-13].

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 tumors.

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 tumors [14]

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.

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 tumors 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 tumors 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[15,16] in a patient presenting with symptoms. Although evidence suggests this relationship persists in a screened [10] population, studies suggest it may not hold true in surveyed patients [17]

Table 1: Current evaluated urinary assays for bladder cancer

Category	Target	Function	Sensitivity	Specificity
Soluble urinary Proteins	- Haemoglobin/red blood cells - Complement factor H-related - NMP-22 - BLCA-1 - BLCA-4 - Survivin - Cytokeratins 8,18,19,20 - Hyaluronic acid and -hyaluronidase	Oxygen carriage Immune system Nuclear structure protein Nuclear structure protein Nuclear structure protein Antiapoptotic protein Cytoskeletal structure Glycosaminoglycan	50-100% 50-100% 50-100% 96% 100% 82-87% 88-94%	Poor 64-100% 75-90% 100% 87-100% 55-70% 84%
Cancer cell-based assays	- Cytology - microsatellite analysis - Telomerase - DNA methylation - FISH to chromsome 3,7,17,9p21 - DD 23 - Karyometry	- Malignant cells - Alterations in DNA microsatellite regions - Telomerase elongating enzyme - Gene regulation - Chromosomal instability - Cancer associated antibody - Chromosomal instability	11-76% 72-97% 70-95% 68-87% 73-100%	>90% >95% 60-70% >90% 33-68%

Several authors have modeled the affect 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 [18,19,20]. These projections use markers with 60–70% sensitivities and higher specificities. More savings could be made by better performing markers. In Egypt, carcinoma of the bladder is the most prevalent first in males representing 16.2% of male cancer [22]. The estimated incidence in males in rural areas in Egypt is about 32 per 100.000 [23].

The exact etiology of bladder cancer is still unknown. Several risk factors have been accused as being involved in its pathogenesis such as cigarette smoking [24], synthetic nitrogen fertilizers [25], organophosphate-based pesticides [26], aromatic amines [8], pelvic irradiation, cyclophosphamide, chronic cystitis, schistosomiasis [24], human papilloma virus [27], genetic

predisposition, and some occupations [24]. The relative importance of such risk factors in the pathogenesis of the disease differs in different populations.

The consensus of opinion and the amount of scientific evidence available from the literature don't suggest that routine or regular screening for bladder cancer is recommended.

Further work should be done for the identification of simple reliable tests that can detect the presence of the disease in high risk patients.

Intervention	Population	Recommendation
Primary Prevention	public	Avoid known carcinogens
Early Detection	public	NOT recommended
Early Detection	- high risk population - history of bladder cancer	- cytology every 2 years - cytology every 6 months

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