Screening for Bladder Cancer

2

Laura-Maria Krabbe, Robert S. Svatek, and Yair Lotan

2.1 Introduction

Bladder cancer is the 4th most common cancer in males (6 % of all cancers diagnosed) and the 11th most common cancer in females in the US in 2013 [1]. Overall, bladder cancer is the sixth most common cancer in the US with 72,570 estimated new cancer cases (54,610 in males and 17,960 in females) and 15,210 estimated deaths (10,820 in males and 4,390 in females) in 2013 [1]. Non-muscle-invasive bladder cancers account for approximately three-fourth of all new diagnosed bladder cancers, and can be subdivided into low-grade and high-grade disease. Low-grade disease usually lacks the tendency to progress into muscle-invasive disease and remains rather indolent and not threatening to survival despite its tendency for frequent recurrence. In contrast, high-grade disease can progress to muscle invasion, which carries a significantly worse prognosis and can lead to severe morbidity due to the need for aggressive therapy to eradicate the disease from the bladder. The lifetime probability (from birth to death) of developing bladder cancer is 3.81 % in males and 1.15 % in females [1]. Depending on the stage of cancer at time of diagnosis the survival rates vary. Unfortunately, approximately one-fourth of all patients present with muscle-invasive or metastatic disease at diagnosis which leads to a poor prognosis for these patients. Patients with organ confined muscle-invasive bladder cancer at diagnosis have an estimated 70 % 5-year survival rate, while the patients with presence of regional or distal metastasis have approximately 33 % and 6 % 5-year survival, respectively [1]. Outcomes for patients with bladder cancer have not significantly improved in the last 25 years, so better methods for detection of bladder cancers before invasion or metastasis as well as better treatment options are needed to improve survival [2].

2.1.1 Basic Rationale for Screening

The concept underlying screening is to diagnose diseases in an asymptomatic population before

L.-M. Krabbe, M.D.
Department of Urology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9110, USA

Department of Urology, University of Muenster Medical Center, Albert-Schweitzer-Campus 1, Gebaeude A1, Muenster, NRW 48149, Germany
e-mail: lauramaria.krabbe@ukmuenster.de

R.S. Svatek, M.D., M.S.C.I.
Department of Urology, University of Texas Health Science Center San Antonio, 7703 Floyd Curl Dr., San Antonio, TX 78229, USA
e-mail: svatek@uthscsa.edu

Y. Lotan, M.D. (✉)
Department of Urology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9110, USA
e-mail: yair.lotan@utsouthwestern.edu

B.R. Konety and S.S. Chang (eds.), *Management of Bladder Cancer: A Comprehensive Text With Clinical Scenarios*, DOI 10.1007/978-1-4939-1881-2_2,
© Springer Science+Business Media New York 2015

symptoms of the disease develop and to improve outcomes compared to the natural history of the disease. One test or a combination of different tests can be used, which should be cost-effective and accurate. Since screening focuses on an asymptomatic population at variable risk for the disease, the invasiveness of the diagnostic tests should be as low as possible so benefits will outweigh risks of screening. The National Cancer Institute published a statement in which three requirements were determined to be fulfilled to have efficacy of screening [3]:

1. Screening leads to earlier disease detection than if the cancer would have been detected because of symptoms.
2. Earlier detection and therefore earlier treatment can improve the overall outcome of the disease.
3. Prospectively collected screening results show a decrease in disease-specific mortality and an improvement in overall survival.

There are potential issues with screening that need to be considered. There is a risk for overdiagnosis of indolent disease which may lead to overtreatment. This is particularly problematic in prostate cancer as diagnosis often results in treatment with either radical prostatectomy or radiation therapy. Therapy for prostate cancer results in significant morbidity and decreased quality of life for many patients due to issues such as erectile dysfunction, urinary incontinence, urinary voiding dysfunction, or anxiety. One potential advantage of screening in bladder cancer is the relative minimal morbidity associated with removing bladder tumors. Second, the accuracy of the screening test is also important since false-positive results can lead to patient anxiety and unnecessary testing with attendant complications and cost. Furthermore, false-negative findings in a cohort at risk may lead to a false sense of security. Finally, benefits of population-based screening should outweigh the risks and show cost-efficacy before widespread utilization.

Interpretation of the benefit of screening based on provided data is subject to important biases termed lead- and length-time bias. Lead-time bias is a statistical distortion of results which can occur because a disease is diagnosed earlier than it would have if it was diagnosed following the onset of symptoms. The additional "lead time" could be falsely interpreted as an increase in survival. Length-time bias occurs because screening studies are more likely to detect patients with slower growing, less aggressive tumors simply because these patients have a longer period of time in the asymptomatic phase than faster growing tumors. Since these slower growing tumors are less likely to result in cancer-related death than the faster-growing tumors, persons with cancer detected through screening will seem to do better than persons with tumor detected without a screening test.

2.1.2 Basic Rationale for Screening for Bladder Cancer

Demographic facts have to be taken into account when discussing screening for bladder cancer. A screening test is most effective when the targeted disease either displays a high incidence or a high mortality [4]. Bladder cancer has a lower incidence and mortality than breast and colon cancer, but higher incidence rates than cervical cancer [1]. However, the incidence rates include all grades (low and high grade) and stages (invasive as well as non-invasive). Since the low-grade cancers are in most cases not life-threatening, their early detection will have minimal impact on survival and the impact of screening on the detection of high-grade or invasive cancers is most critical [2]. Based on the current incidence and the fact that low-grade non-invasive tumors constitute approximately 40–50 % of all bladder cancers, screening the whole population is unlikely to be effective. In order for bladder cancer screening to be considered, a high-risk cohort needs to be identified. There are several well-known risk factors for bladder cancer including increasing age and male gender [1]. The risk to develop bladder cancer increases significantly with rising age (probability of developing bladder cancer: 0.37 % in men under 60 years old and 3.69 % in men over 70 years old). Also the incidence of bladder cancer is significantly higher in men (37.5/100,000 men vs. 9.3/100,000 women).

Most bladder cancers result from smoking or less frequently environmental exposures. Risk factors for bladder cancer can be acquired through exposure to a carcinogen such as cigarette smoke, aromatic amines, or polycyclic aromatic hydrocarbons [5, 6]. These carcinogens can be subdivided in occupational (aromatic amines, polycyclic aromatic hydrocarbons) and non-occupational risk factors (smoking). Smokers have a four- to fivefold higher risk of developing bladder cancer compared to non-smokers [5]. Other risk factors can be determined genetically, like a positive family history or known predisposing syndromes like the Lynch Syndrome [7–9]. The probability of overdiagnosis of bladder cancer with screening seems negligible since invasive bladder cancers found at autopsies are extremely rare, suggesting that most invasive cancers become symptomatic in a rather short timeframe [10].

2.2 Urine Markers: What Possible Tools Do We Have And How Good Are They?

At this time bladder cancer is diagnosed in patients who are found to have blood in the urine. As such, the most commonly used tool to screen for bladder cancer has been to look for microscopic blood in the urine. Several urine-based tumor markers have also been investigated for their potential role in screening for bladder cancer, detection of bladder cancer in patients with micro-hematuria as well as for surveillance of recurrent bladder cancer. To date, none of them could demonstrate sufficient performance (sensitivity, specificity, and positive predictive value) to be recommended for screening. In this chapter, we will review the data available for tests that have been previously utilized for bladder cancer screening.

2.2.1 Dipstick Hematuria Testing

Dipstick testing of freshly voided urine is used commonly to evaluate the presence or absence of micro-hematuria, is inexpensive and gives immediate results. It can be done in the office or at home by the patients themselves after only little training. The test does not require intact red blood cells and can detect micro-hematuria with a sensitivity of 0.91 and a specificity of 0.99 [11, 12].

Unfortunately, there is a high prevalence of microscopic hematuria in the adult population (as high at 10–14 %) and most do not have bladder cancer with rates of 2–5 % in referred populations [13]. As such, the low positive predictive value (PPV) results in many unnecessary workups with resultant cost and anxiety. Unfortunately, dipstick performance in detection of bladder cancer is even less effective and results in a sensitivity of 0.52 and a specificity of 0.82 over all stages and grades [14]. Sensitivity is better for higher grade and higher stages of disease.

2.2.2 Cytology

Cytology is used high frequently to assess malignant, suspicious, or atypical cells in voided urine samples. It is a subjective procedure with high intra-observer variability and the results are not available immediately. Overall sensitivity of cytology is very low (approximately 34 %) but can be as high as 80–90 % for high-grade disease. It benefits form a very high specificity of 95–99 % which exceeds all available markers [14]. Cytology has not been studied sufficiently in the screening setting to determine its performance, especially when considering that many screened tumors may be smaller than those detected symptomatically. Furthermore, the test is relatively expensive since requires preparation and a pathologist to interpret results.

2.2.3 Nuclear Matrix Protein 22 (NMP-22)

The BladderChek NMP-22 test (Alere Inc., Waltham, MA, USA) is a point-of-care assay in which freshly voided urine is tested for presence or absence of nuclear matrix proteins, which are preferentially released into the urine during cell destruction as commonly present in malignancies.

Because of its superior sensitivity compared to cytology, the US food and drug administration (FDA) approved NMP-22 for detection of bladder cancer in patients with hematuria and surveillance of patients with a positive history of bladder cancer [15, 16]. Overall sensitivity is 0.73 and specificity is 0.80, also with better performance in higher grades and higher stages [14]. As other markers, the performance of NMP-22 has been primarily assessed in patients with bladder cancer or at risk for bladder cancer and needs to be better defined in a screened population.

2.2.4 Fluorescence In Situ Hybridization Assay (FISH)

The UroVysion FISH assay (Abbott Inc., Abbott Park, IL, USA) is a laboratory multi-target essay that detects aneuploidy of chromosomes 3, 7, and 17 as well as loss of 9p21 and in cells in voided urine with an overall sensitivity of 0.71 in patients with a history of bladder cancer and a specificity of 0.95 in healthy volunteers without a history of bladder cancer [17]. The specificity is generally lower in patients undergoing evaluation for bladder cancer (between 0.84 and 0.94) [18]. Furthermore, the lab-based assays have a considerably higher cost then point-of-care tests and this has a detrimental impact on their cost-effectiveness in the setting of screening large populations.

2.2.5 ImmunoCyt Test

Bladder cancer markers present on exfoliated cells in voided urine are detected by various fluorescent antibodies (19A211, M344, and LDQ10) of the ImmunoCyt test (DiagnocureInc, Québec, QB, Canada/Scimedx, Denville, NJ, USA) and evaluated in conjunction with cytology. This test is FDA-approved for surveillance of bladder cancer and not for detection at this time. Unfortunately this test is a laboratory test only, but reaches a sensitivity of 0.86 and a specificity of 0.79. Noteworthy is its overall good performance regardless of grade or stage of the tumors [19].

2.2.6 Bladder Tumor Antigen (BTA)

BTA-Stat and BTA-Trak are semi-quantitative and quantitative immunoassays detecting complement factor H (CFH) and related proteins (CFH-rp) in voided urine as a point-of-care test [20, 21]. BTA-Stat has a sensitivity of 0.71 and a specificity of 0.73 whereas BTA-Trak has a sensitivity of 0.69 and a specificity of 0.90 overall [14]. Best performance of both tests is in detection of tumors with higher grades and higher stages [14].

2.3 Screening for Bladder Cancer: What Data Is Out There?

2.3.1 Screening of the General Population

There have been only few studies investigating screening for bladder cancer in the general population (Table 2.1). Messing et al. tested 1,575 men (45 % of men solicited), older than 50 years for hematuria via repetitive home screening with urine dipstick testing [22]. The patients were advised to carry out daily urine testing for 14 days and if results were all negative, to repeat testing 9 months later for another 14 days. Patients with one or more positive tests were recommended to have a complete workup including intravenous urogram, cystoscopy, and cytology. A control group ($n=509$) was formed with data from the Wisconsin Cancer Reporting System (WCRS) which is a population-based tumor registry. Screening and control population had a similar mean age of 64.8 and 64.0 years and a comparable amount of smokers 15.9 and 22.0 % for current smokers at the time of study and 44.0 and 47.0 % former smokers. In the screening group 258 (16.4 %) men had positive dipstick testing and underwent evaluation as mentioned above. A total of 21 bladder cancers (1.33 %) were found on these evaluations and were treated according to tumor stage and grade. There was no significant difference found in the detected bladder cancers in proportion of low-grade and

Table 2.1 Screening for bladder cancer in the general population and heavy smokers

Study author	Country	Study time	Population targeted	No. of total patients in study	Primary test	No. of positive tests (%)	Further tests	No. of positive further tests (%)	Diagnostic procedure	No. of diagnostic procedures	No. of bladder cancer found	% of bladder cancer found in total population
General population												
Messing et al. [22]	USA	1989–1992	Men >50 years	1,575	Dipstick	258 (16.4)	–	–	Cystoscopy	258	21	1.33
Britton et al. [24]	UK	1989–1992	Men >60 years	2,356	Dipstick	474 (20.1)	–	–	Cystoscopy	317	17	0.72
Hedelin et al. [26]	Sweden	Before 2006	Men 60–70 years	1,096	Dipstick	174 (15.9)	–	–	Cystoscopy (white-light + fluorescent)	174	7	0.64
Bangma et al. [31]	The Netherlands	2008–2009	Men 50–75 years	1,747	Dipstick/UBC	409 (23.4)	NMP-22, MA, FGFR3, CH3	75 (18.3)	Cystoscopy	71	4	0.23
Total	–	–	Men >50 years	6.774	Dipstick	1.315 (19.4)	–	–	Cystoscopy	820	49	0.72
Heavy smokers												
Steiner et al. [35]	Austria	2007	Smokers ≥40 PY	183	Dipstick, NMP-22, Cytology, FISH	75 (40, 9)	–	–	Cystoscopy	75	3	1.64
Lotan et al. [36]	USA	2006–2007	>50 years, smoking >10 years, occupational exposure >15 years	1,502	NMP-22	85 (5.7)	–	–	Cystoscopy	69	3[a]	0.13
Total	–	–	Heavy smokers	1,685	Various	160 (9.4)	–	–	Cystoscopy	144	6	0.36

[a]1 marked atypia

high-grade cancers between the screening (52.4 % vs. 47.7 %) and control group (60.3 % vs. 39.7 %), but the proportion of invasive high-grade cancers was significantly lower in the screening group (10 % vs. 60 % of all high-grade tumors detected and 4.8 % vs. 23.5 % of all cancers detected, $p=0.02$) [23]. The long-term outcomes showed that none of the men who had a cancer detected through screening died of bladder cancer, while 20.4 % of the patients with bladder cancer in the control group died of disease ($p=0.02$) and suggested a significant reduction in mortality from bladder cancer.

In a similar effort Britton et al. screened 2,356 men, older than 60 years, with weekly urine dipstick testing for a total of 10 weeks, without any repeat testing when results were negative [24]. Similar to Messing et al. [22], 474 (20 %) had a positive urine dipstick for hematuria and 319 underwent evaluation of hematuria. There were 17 (0.7 % of total study population and 3.5 % of men with hematuria) patients diagnosed with bladder cancer (out of which ten men had a positive cytology). As in the Messing cohort, approximately 53 % (9 of 17) of patients had high-grade disease but screening resulted in a significant reduction in the detection of muscle-invasive disease with no patients found by Britton to have muscle-invasive disease. Outcome results did not match the results of the Messing study however, since five of nine (56 %) patients with high-grade bladder cancer progressed to muscle-invasive bladder cancer, and three (33.3 %) died of disease as well as three died from unrelated causes [25]. No control group was available in this study, so understaging at the time of diagnosis or undertreatment of disease for high-grade tumors is a possibility.

In 2006, Hedelin et al. reported about a cohort of asymptomatic men (age 60–70 years) from Scandinavia [26]. They included 1,096 (55 % of invited men) and used urine dipstick, urinary bladder cancer test (UBC), and international prostate symptom score (IPSS) as screening tools. Patients with a positive urine test or IPSS >10 were evaluated with white-light and fluorescence cystoscopy. Seven tumors were detected with white-light cystoscopy, all in patients that had a history of smoking (two in patients without hematuria, but positive UBC test). No additional tumors were detected with fluorescence cystoscopy. The authors concluded that UBC and fluorescence cystoscopy were not useful in screening, and the high rate of micro-hematuria (25 %), without corresponding malignant disease, made screening of the general population ineffective.

The most recent study comes out of the Netherlands. With the aim to see if general population screening is feasible and to find a way to reduce cystoscopies, Roobol et al. initiated a prospective trial in which Dutch men aged 50–75 could participate [27]. A total of 6,500 men were invited to participate and were trained to conduct 14 consecutive, daily home urine dipstick testing. If one or more results were positive, participants were recommended to undergo further evaluation consisting of more urine tests using molecular markers in the first instance. Further urine tests consisted of NMP-22, microsatellite analysis (MA), fibroblast growth factor receptor (FGFR3), and multiplex ligation-dependent probe amplifications (MLPA) [28–30]. Recently, the final results were reported [31] with 1,747 men undergoing hematuria testing of which 409 men (23.4 %) tested positive with urine dipstick. Of these, 385 (94.1 %) men underwent subsequent testing for the other urine markers mentioned and 75 (18.3 %) had one or more positive test results and were referred for cystoscopy. Cystoscopy was performed on 71 (94.7 %) subjects and four bladder cancers (0.2 % of total population tested and 1 % of men with positive dipstick) and one kidney tumor were detected. Patients with positive markers, but negative cystoscopy were asked to undergo rescreening 6 months later. From linkage with the Dutch Cancer Registry one bladder cancer and one kidney cancer were missed by the screening protocol. Interestingly, three of four detected bladder cancers by protocol were in non-smokers, whereas the cohort had 58 % former smokers and 17.1 % current smokers. Also 36 % of the cohort stated a history of occupational exposures, but there was no significant difference between positive dipstick or positive molecular markers and smoking or occupational exposure. While use of a second-step combination of molecular urine markers resulted

in a significant reduction of cystoscopies with very few missed cancers, the low number of cancers detected and high cost demonstrated minimal benefit of screening an asymptomatic unselected population.

2.3.2 Screening of Non-occupational High-Risk Populations

Targeted screening of high-risk patients increases the cancer yield and reduces the number of unnecessary evaluations. Identification of risk is an important component of screening for all cancers. Age is the primary risk factor in deciding when to screen for colon, breast and prostate cancer since cancer is typically a disease of the elderly. Similarly, any strategy to screen for bladder cancer will require a determination of risk and will be limited to the highest risk cohort, which will allow screening to be practical and cost-effective.

2.3.2.1 Definition of High-Risk Populations

As mentioned above (Sect. 2.2) various risk factors increase the chance for developing bladder cancer. A positive family history generates a two- to sixfold increased relative risk (RR) to develop bladder cancer, but this only accounts for around 2 % of total bladder cancer diagnoses [7]. Also tumor predisposing syndromes like the Lynch syndrome (see section "Screening in Patients with Lynch syndrome") increase the RR for developing bladder cancer up to 5.42 depending on genetic mutation present [3]. Non-genetic, acquired risk factors include smoking, occupational exposure and others like certain medications (thiazolidinediones, cyclophosphamide, and phenacetin), radiation exposure, exposure to herbs containing aristolochic acids, infections and chronic irritation due to indwelling catheters. Smoking is the leading cause of bladder cancer with an increased RR for former and current smokers (defined as >10 cigarettes/day). RR for current smokers is 4–5 times higher than for non-smokers and even former smokers kept an increased RR of 1.3–2.7 for men and 1.8–3.8 for women, depending on intensity of former smoking, with the tendency to persist through time after quitting [5, 32]. Occupational exposure to aromatic amines or polycyclic aromatic hydrocarbons has an elevated RR between 1.16 and 1.23. The attributable risk is the amount of disease incidence that can be attributed to a specific exposure. Attributable risk is calculated by taking the difference in incidence of disease between exposed and non-exposed individuals. The attributable risk of bladder cancer from occupational exposures is 4.2–7.4 % [33]. There is also a gender and age-associated risk with men and older subjects exhibiting higher rates of bladder cancer as noted previously.

There have been attempts to quantify the degree of risk by establishing predictive models. A study by Wu et al. including 678 white bladder cancer patients and 678 controls found that significant risk factors for bladder cancer included pack-years smoked and exposures to diesel, aromatic amines, dry cleaning fluids, radioactive materials, and arsenic [34]. This model yielded good discriminatory ability (AUC = 0.70; 95 % CI, 0.67–0.73) but improved to 0.80 (95 % CI, 0.72–0.82) when mutagen sensitivity data were incorporated. Mutagen analysis is expensive at this time and may not be practical for broad-based screening. Furthermore, this will need to be validated in prospective studies. Decision-analysis techniques were applied by Vickers et al. based on the occurrence of high-grade or invasive bladder cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) [7]. The PLCO included 149,619 individuals of 55–75 years of age and a risk score for bladder cancer was defined that consisted of four variables that could sum up to reach 0–11 points total (2 points for age >65; 2 points for smoking history >10–19 pack-years, 4 points for smoking history >20 pack-years, 4 points for male sex and 1 point for positive family history). If people with >6 points (around 25 % of the population) were screened for bladder cancer, 57 cases of high-grade or invasive bladder cancer per 100,000 people could be detected. Screening the total population would detect only 38 further cases at

much higher costs. The assumption is that earlier detection would also reduce mortality if the cases can be identified before the cancer became invasive.

2.3.2.2 Evidence of Screening on high-risk populations

Few studies have been published concerning high-risk populations for bladder cancer. Two groups have presented results of screening in a high-risk smoking population (Table 2.1) and very diverse studies have shown conflicting results in screening people with occupational exposure (Table 2.2).

2.3.2.2.1 Heavy Smokers and Occupational Exposed People

The rationale for screening heavy smokers is that the majority of patients with bladder cancer are previous or current smokers and tobacco exposure is the most significant risk factor for the disease. Steiner et al. screened 183 heavy smokers (>40 pack years) using urine dipstick test, NMP-22, cytology, and FISH [35]. Participants with one or more positive test results were further evaluated including cystoscopy and imaging. Seventy-five men (40.9 %) had one or more positive test results and in further evaluation, 18 men (24 % of men with positive test results and 9.8 % of total cohort) were detected as having an abnormal histologic condition. Of those lesions 15 were in the urinary bladder (1 pT1 low-grade, 2 carcinoma in situ (CIS), 11 dysplastic lesions, and 1 inverted papilloma) and 2 upper tract urothelial tumors and 1 renal cell carcinoma. Thus a total of 6 men (3.3 %) had urinary tract malignancy and 12 (6.6 %) displayed a possible precancerous lesion of the urinary tract. The authors considered screening of this population efficient and the most efficient screening tool was the combination of FISH, cytology and urine dipstick testing. However, there are questions regarding cost implications of using multiple tests and their incidence of disease far exceeded that of any other screening study to date.

A larger study by Lotan et al. screened a high-risk population, defined as ≥10 years history of smoking ($n=1{,}298$) or ≥15 years of occupational status ($n=513$) using the NMP-22 BladderChek test [36]. In case of a positive NMP-22 result, the participants were advised to undergo evaluation with cystoscopy and cytology. NMP-22 was positive in 85 participants (5.7 %) and 69 underwent further evaluation, the other 16 declined. Of those that underwent further testing, three (3.5 %) participants were found to have lesions, including one pTa high grade, one pTa low grade, and one marked atypia. This represented 0.16 % of the total cohort. In the 12 months of follow-up period (range 0.9–25.5 months), 2 of 1,309 (0.15 %) participants developed low-grade non-invasive bladder cancer. The low incidence of cancer suggests that the selection criteria for bladder cancer risk were too low. Furthermore, women were included in the screening ($n=327$) and all the cancers were confined to men.

Occupational exposure is known to increase the risk for development of bladder cancer. Still, various studies on screening of workers have shown that bladder cancer incidence is low and those studies lack information regarding time of exposure and smoking histories. Furthermore, they frequently were underpowered due partly to low acceptance rates of workers for screening (Table 2.2) [37–44]. While regulations have reduced exposure to potential carcinogens in the Western world, there is still concern for potential exposures in developing societies.

2.3.2.2.2 Aristolochic Acid

Zlotta et al. reported about screening a cohort of persons that had been exposed to aristolochic acid (present in certain Chinese herbs) and were diagnosed with aristolochic acid nephropathy (AAN) [45]. Patients exposed to aristolochic acid show a rapidly progressive renal interstitial fibrosis alongside with renal failure as well as a high incidence of upper tract urothelial cancers and bladder cancers. In their study, a total of 43 patients were screened for bladder cancer biannually for 10 years via cystoscopy and mapping biopsies. Bladder cancer was diagnosed in 25 patients (52 %). The vast majority (22 patients) were diagnosed with non-muscle-invasive cancer and none

Table 2.2 Screening for bladder cancer in workers

Study author	Country	Study time	Population targeted	No. of total patients in study	Primary test	No. of positive tests (%)	Diagnostic procedure	No. of diagnostic procedures	No. of Bladder cancer found	% of Bladder cancer found in total population
Davies et al. [37]	UK	1970	Workers	4,636	Urine microscopy	84 (1.8)	Repeat urine-test and Cystoscopy	–	3	0.06
Pesch et al. [38]	Germany	2003–2010	Workers exposed to AA	1,323[a]	Dipstick, Urine-sediment, Cytology, NMP-22, FISH	493 (37.2)	Cystoscopy	–	14[b]	1.06
Crosby et al. [39]	USA	Before 1991	Workers exposed to AA	541	Cytology	64 (11.8)	Cystoscopy	24	7	1.29
Marsh and Cassidy [40]	USA	1986–2001	Workers exposed to AA	277	Urinalysis, Cytology, Quantitative Fluorescence	51 (18.4)	Cystoscopy	40	3	1.08
Hemstreet et al. [41]	China	1991–1997	Workers exposed to B	1,788	Dipstick, Cytology, DNA ploidy, p300	153 (8.6 %)	Cystoscopy	116	28	1.57
Ward et al. [42]	USA	1969–1979	Workers exposed to BD	385	Dipstick, Cytology	60 (15.6)	Cystoscopy	200	3	0.78
Chen et al. [43]	Taiwan	Before 2005	Workers exposed to BD	70	Dipstick, Cytology, NMP-22	15 (21.4)	Cystoscopy	15	0	0.00
Giberti et al. [44]	Italy	2006–2008	Workers exposed to PAH	152	Dipstick, Cytology, ImmunoCyt	18 (11.8)	Cystoscopy	18	0	0.00
Total	–	–	Workers exposed to AA, B, BD, PAH	9,172	Dipstick, Cytology and others	938 (29, 37)	Cystoscopy	413	58	0.63

AA aromatic amines, *B* benzidine, *BD* benzidine derivates, *PAH* polycyclic aromatic hydrocarbons
[a]21 patients with history of BC included
[b]3 patients with history of BC

died of bladder cancer. However, three patients declined further screening and subsequently developed muscle-invasive and metastatic disease and died from bladder cancer. These results suggest that aggressive screening (consisting of urine markers alongside cystoscopy) in a population with these high incidences of bladder cancer and urothelial carcinoma in general seems obligate and effective.

2.3.2.2.3 Screening in Patients with Lynch Syndrome

Patients with Lynch syndrome express mutations in MLH1 and MSH2 (90 %) as well as MSH6 (10 %) and are at high risk of developing various cancers, which differ by mutation present [46]. These patients have the highest risk of developing colorectal cancer and endometrial cancer alongside with ovarian cancer, with age and mutation-dependent cumulative risks up to 49 % for colorectal cancer, 57 % for endometrial cancer and 38 % for ovarian cancer. But also other cancer entities are found more frequently in patients with Lynch syndrome like gastric cancer, small bowel cancer, biliary tract cancer, and urothelial cancer. Cumulative risk for urothelial cancer at the age of 70 years is estimated to a total of 1.9 % over all mutations, but up to 8 % for MSH2 mutations. In a recent publication by Skeldon et al., cancer incidences of patients with Lynch syndrome were compared to the general Canadian population and bladder cancer as well as upper tract urothelial cancer (UTUC) incidences were significantly higher in patients with MSH2 mutation (6.21 % for bladder cancer and 3.95 % for UTUC, both $p < 0.001$), but without statistical significance for MLH1 mutations [47]. Since patients and families with Lynch syndrome are under close observation for different cancers, patients with MSH2 mutations should be offered screening for bladder cancer and UTUC. Which testing and at what intervals has yet to be defined. Because of the considerably lower incidence of bladder cancer in the other mutations (MLH1 and MSH6), it will be important to consider the cost-benefit of screening these patients.

2.4 Cost and Cost-Effectiveness of Screening for Bladder Cancer

Cost and cost-effectiveness research is an important consideration when evaluating the feasibility and practicality of screening for bladder cancer. Currently, bladder cancer is estimated to cost approximately $3.98 billion and estimates have been projected at nearly $5 billion by 2020 (in 2010 dollars) [48].

Screening for other cancers such as breast and prostate cancer is widely practiced and from a cost perspective is considered reasonable but can result in costs up to US$50,000 per life year saved [49, 50]. Prevalence of disease, benefit of screening, performance of the test used and costs of the test play into the calculation, because a more expensive test has to perform significantly better than a cheaper test in order to maintain cost-effectiveness [51]. Cost for urine marker tests vary significantly with point of care tests such as NMP-22 BladderChek test or BTA stat costing approximately US$20–24 in comparison with laboratory tests such as FISH or ImmunoCyt that account for over US$200 per test. With lack of prospective studies up until now looking at cost-effectiveness of screening for bladder cancer, decision-analytic models are used to determine benefit of screening, which has the advantage of being able to vary certain factors such as marker cost, incidence of disease, and marker performance [51]. A Markov model, used to estimate cumulative cancer-related costs and efficacy of screening vs. no screening of a high-risk population for bladder cancer using a urine-based marker over a 5-year period, found that screening in a population with a bladder cancer incidence of >1.6 % would improve overall survival as well as result in potential cost savings [52]. This is unique and is bound to the fact that detecting high-grade tumors before muscle invasion results in survival advantage and also a cost-benefit due to lower costs for treatment of non-muscle-invasive tumors (transurethral resection of bladder tumors (TUR-BT) and intravesical therapy including follow up) compared to muscle-invasive tumors

(cystectomy in combination with chemotherapy). Still, these results depend highly on cancer incidence. The relatively low incidence of bladder cancer, even in high-risk populations, remains the biggest challenge for a screening paradigm. Also performance of the markers used weigh heavily into the equation. While a higher sensitivity improves cost-effectiveness by improving survival due to earlier detection of cancer, a higher specificity increases cost-effectiveness by decreasing the number of unnecessary work-ups [51]. Also, cost of the test used has a major influence on cost-effectiveness for screening, since the cost of every test used will be transferred to each person screened.

2.5 Conclusions and Perspectives

Though screening for bladder cancer may be feasible in high-risk populations, there is currently no significant evidence to recommend such, because of lack of sufficient data to define screening protocols as well as lack of availability of high-performance urine markers reaching cost-effectiveness. There are few exceptions in which screening should be considered, consisting of patients with AAN due to their extremely elevated risk of urothelial disease. Furthermore, patients with Lynch syndrome and verified mutation of MSH2 likely have sufficient risk to justify screening for bladder cancer but the best screening practice is yet to be determined.

Demonstration of a survival benefit or at a minimum downstaging from muscle invasion to non-muscle-invasive disease is necessary before bladder cancer screening can be recommended. To demonstrate this would require a large prospective study targeting a population at sufficient risk and would ideally incorporate a cost-effective endpoint. One advantage of screening in bladder cancer however, unlike prostate cancer, is that the risks associated with unnecessary work-ups may be costly but have minimal risks. In prostate cancer the damage of unnecessary screening includes all the negative consequences associated with prostate cancer diagnosis and treatment such as erectile dysfunction, urinary incontinence, and anxiety.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63(1):11–30. Epub 2013/01/22.
2. Larre S, Catto JW, Cookson MS, Messing EM, Shariat SF, Soloway MS, et al. Screening for bladder cancer: rationale, limitations, whom to target, and perspectives. Eur Urol. 2013;63(6):1049–58. Epub 2013/01/15.
3. NCI. NCI cancer screening overview. 2007. http://www.cancer.gov/cancerinfo/pdq/screening/overview. Accessed 26 Aug 2007.
4. Wilson J, Jungers GE. Principles and practice of screening for disease. Geneva, Switzerland: World Health Organization; 1968. p. 163.
5. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA. 2011;306(7):737–45. Epub 2011/08/19.
6. Silverman DT, Hartge P, Morrison AS, Devesa SS. Epidemiology of bladder cancer. Hematol Oncol Clin North Am. 1992;6(1):1–30. Epub 1992/02/01.
7. Vickers AJ, Bennette C, Kibel AS, Black A, Izmirlian G, Stephenson AJ, et al. Who should be included in a clinical trial of screening for bladder cancer? A decision analysis of data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Cancer. 2013;119(1):143–9. Epub 2012/06/28.
8. Garcia-Closas M, Malats N, Silverman D, Dosemeci M, Kogevinas M, Hein DW, et al. NAT2 slow acetylation, GSTM1 null genotype, and risk of bladder cancer: results from the Spanish Bladder Cancer Study and meta-analyses. Lancet. 2005;366(9486):649–59. Epub 2005/08/23.
9. Engel C, Loeffler M, Steinke V, Rahner N, Holinski-Feder E, Dietmaier W, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012;30(35):4409–15. Epub 2012/10/24.
10. Kishi K, Hirota T, Matsumoto K, Kakizoe T, Murase T, Fujita J. Carcinoma of the bladder: a clinical and pathological analysis of 87 autopsy cases. J Urol. 1981;125(1):36–9. Epub 1981/01/01.
11. Messing EM, Young TB, Hunt VB, Wehbie JM, Rust P. Urinary tract cancers found by homescreening with hematuria dipsticks in healthy men over 50 years of age. Cancer. 1989;64(11):2361–7. Epub 1989/12/01.
12. Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, et al. Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation. Health Technol Assess. 2006;10(18):iii–iv, xi-259. Epub 2006/05/30.

13. Buteau A, Seideman CA, Svatek RS, Youssef RF, Chakrabarti G, Reed G, et al. What is evaluation of hematuria by primary care physicians: use of electronic medical records to assess practice patterns with intermediate follow-up. Urol Oncol. 2014;32:128–34. Epub 2012/11/17.
14. Lotan Y, Roehrborn CG. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: results of a comprehensive literature review and meta-analyses. Urology. 2003;61(1):109–18. Discussion 18. Epub 2003/02/01.
15. Grossman HB, Messing E, Soloway M, Tomera K, Katz G, Berger Y, et al. Detection of bladder cancer using a point-of-care proteomic assay. JAMA. 2005;293(7):810–6. Epub 2005/02/17.
16. Grossman HB, Soloway M, Messing E, Katz G, Stein B, Kassabian V, et al. Surveillance for recurrent bladder cancer using a point-of-care proteomic assay. JAMA. 2006;295(3):299–305. Epub 2006/01/19.
17. Sarosdy MF, Schellhammer P, Bokinsky G, Kahn P, Chao R, Yore L, et al. Clinical evaluation of a multitarget fluorescent in situ hybridization assay for detection of bladder cancer. J Urol. 2002;168(5):1950–4. Epub 2002/10/24.
18. Lotan Y, Bensalah K, Ruddell T, Shariat SF, Sagalowsky AI, Ashfaq R. Prospective evaluation of the clinical usefulness of reflex fluorescence in situ hybridization assay in patients with atypical cytology for the detection of urothelial carcinoma of the bladder. J Urol. 2008;179(6):2164–9. Epub 2008/04/22.
19. Messing EM, Teot L, Korman H, Underhill E, Barker E, Stork B, et al. Performance of urine test in patients monitored for recurrence of bladder cancer: a multicenter study in the United States. J Urol. 2005;174(4 Pt 1):1238–41. Epub 2005/09/08.
20. Sarosdy MF, Hudson MA, Ellis WJ, Soloway MS, deVere WR, Sheinfeld J, et al. Improved detection of recurrent bladder cancer using the Bard BTA stat Test. Urology. 1997;50(3):349–53. Epub 1997/09/25.
21. Thomas L, Leyh H, Marberger M, Bombardieri E, Bassi P, Pagano F, et al. Multicenter trial of the quantitative BTA TRAK assay in the detection of bladder cancer. Clin Chem. 1999;45(4):472–7. Epub 1999/04/02.
22. Messing EM, Young TB, Hunt VB, Gilchrist KW, Newton MA, Bram LL, et al. Comparison of bladder cancer outcome in men undergoing hematuria home screening versus those with standard clinical presentations. Urology. 1995;45(3):387–96. Discussion 96–7. Epub 1995/03/01.
23. Messing EM, Madeb R, Young T, Gilchrist KW, Bram L, Greenberg EB, et al. Long-term outcome of hematuria home screening for bladder cancer in men. Cancer. 2006;107(9):2173–9. Epub 2006/10/10.
24. Britton JP, Dowell AC, Whelan P, Harris CM. A community study of bladder cancer screening by the detection of occult urinary bleeding. J Urol. 1992;148(3):788–90. Epub 1992/09/01.
25. Mayfield MP, Whelan P. Bladder tumours detected on screening: results at 7 years. Br J Urol. 1998;82(6):825–8. Epub 1999/01/12.
26. Hedelin H, Jonsson K, Salomonsson K, Boman H. Screening for bladder tumours in men aged 60-70 years with a bladder tumour marker (UBC) and dipstick-detected haematuria using both white-light and fluorescence cystoscopy. Scand J Urol Nephrol. 2006;40(1):26–30. Epub 2006/02/03.
27. Roobol MJ, Bangma CH, el Bouazzaoui S, Franken-Raab CG, Zwarthoff EC. Feasibility study of screening for bladder cancer with urinary molecular markers (the BLU-P project). Urol Oncol. 2010;28(6):686–90. Epub 2010/11/11.
28. van Oers JM, Lurkin I, van Exsel AJ, Nijsen Y, van Rhijn BW, van der Aa MN, et al. A simple and fast method for the simultaneous detection of nine fibroblast growth factor receptor 3 mutations in bladder cancer and voided urine. Clin Can Res. 2005;11(21):7743–8. Epub 2005/11/10.
29. van Rhijn BW, Lurkin I, Kirkels WJ, van der Kwast TH, Zwarthoff EC. Microsatellite analysis–DNA test in urine competes with cystoscopy in follow-up of superficial bladder carcinoma: a phase II trial. Cancer. 2001;92(4):768–75. Epub 2001/09/11.
30. Zuiverloon TC, Beukers W, van der Keur KA, Munoz JR, Bangma CH, Lingsma HF, et al. A methylation assay for the detection of non-muscle-invasive bladder cancer (NMIBC) recurrences in voided urine. BJU Int. 2012;109(6):941–8. Epub 2011/07/16.
31. Bangma CH, Loeb S, Busstra M, Zhu X, Bouazzaoui SE, Refos J, et al. Outcomes of a bladder cancer screening program using home hematuria testing and molecular markers. Eur Urol. 2013;64:41–7. Epub 2013/03/13.
32. Welty CJ, Wright JL, Hotaling JM, Bhatti P, Porter MP, White E. Persistence of urothelial carcinoma of the bladder risk among former smokers: Results from a contemporary, prospective cohort study. Urol Oncol. 2014;32:25.e21–5. Epub 2013/03/20.
33. Kogevinas M, 'tMannetje A, Cordier S, Ranft U, Gonzalez CA, Vineis P, et al. Occupation and bladder cancer among men in Western Europe. Cancer Causes Control CCC. 2003;14(10):907–14. Epub 2004/01/31.
34. Wu X, Lin J, Grossman HB, Huang M, Gu J, Etzel CJ, et al. Projecting individualized probabilities of developing bladder cancer in white individuals. J Clin Oncol. 2007;25(31):4974–81. Epub 2007/11/01.
35. Steiner H, Bergmeister M, Verdorfer I, Granig T, Mikuz G, Bartsch G, et al. Early results of bladder-cancer screening in a high-risk population of heavy smokers. BJU Int. 2008;102(3):291–6. Epub 2008/03/14.
36. Lotan Y, Elias K, Svatek RS, Bagrodia A, Nuss G, Moran B, et al. Bladder cancer screening in a high risk asymptomatic population using a point of care urine based protein tumor marker. J Urol. 2009;182(1):52–7. Discussion 8. Epub 2009/05/20.

37. Davies M. Final diagnoses after urinary screening of apparently normal workmen. Proc R Soc Med. 1970;63(3):242. Epub 1970/03/01.
38. Pesch B, Nasterlack M, Eberle F, Bonberg N, Taeger D, Leng G, et al. The role of haematuria in bladder cancer screening among men with former occupational exposure to aromatic amines. BJU Int. 2011;108(4):546–52. Epub 2011/01/13.
39. Crosby JH, Allsbrook Jr WC, Koss LG, Bales CE, Witherington R, Schulte PA, et al. Cytologic detection of urothelial cancer and other abnormalities in a cohort of workers exposed to aromatic amines. Acta Cytol. 1991;35(3):263–8. Epub 1991/05/01.
40. Marsh GM, Cassidy LD. The Drake Health Registry Study: findings from fifteen years of continuous bladder cancer screening. Am J Ind Med. 2003;43(2):142–8. Epub 2003/01/24.
41. Hemstreet 3rd GP, Yin S, Ma Z, Bonner RB, Bi W, Rao JY, et al. Biomarker risk assessment and bladder cancer detection in a cohort exposed to benzidine. J Natl Cancer Inst. 2001;93(6):427–36. Epub 2001/03/22.
42. Ward E, Halperin W, Thun M, Grossman HB, Fink B, Koss L, et al. Screening workers exposed to 4,4′-methylenebis(2-chloroaniline) for bladder cancer by cystoscopy. J Occup Med. 1990;32(9):865–8. Epub 1990/09/01.
43. Chen HI, Liou SH, Loh CH, Uang SN, Yu YC, Shih TS. Bladder cancer screening and monitoring of 4,4′-methylenebis(2-chloroaniline) exposure among workers in Taiwan. Urology. 2005;66(2):305–10. Epub 2005/08/16.
44. Giberti C, Gallo F, Schenone M, Genova A. Early results of urothelial carcinoma screening in a risk population of coke workers: urothelial carcinoma among coke workers. Biomed Environ Sci BES. 2010;23(4):300–4. Epub 2010/10/12.
45. Zlotta AR, Roumeguere T, Kuk C, Alkhateeb S, Rorive S, Lemy A, et al. Select screening in a specific high-risk population of patients suggests a stage migration toward detection of non-muscle-invasive bladder cancer. Eur Urol. 2011;59(6):1026–31. Epub 2011/04/05.
46. Bonadona V, Bonaiti B, Olschwang S, Grandjouan S, Huiart L, Longy M, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011;305(22):2304–10. Epub 2011/06/07.
47. Skeldon SC, Semotiuk K, Aronson M, Holter S, Gallinger S, Pollett A, et al. Patients with Lynch syndrome mismatch repair gene mutations are at higher risk for not only upper tract urothelial cancer but also bladder cancer. Eur Urol. 2013;63(2):379–85. Epub 2012/08/14.
48. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst. 2011;103(2):117–28. Epub 2011/01/14.
49. Redaelli A, Cranor CW, Okano GJ, Reese PR. Screening, prevention and socioeconomic costs associated with the treatment of colorectal cancer. Pharmacoeconomics. 2003;21(17):1213–38. Epub 2004/02/28.
50. Krahn MD, Coombs A, Levy IG. Current and projected annual direct costs of screening asymptomatic men for prostate cancer using prostate-specific antigen. CMAJ Can Med Assoc J. 1999;160(1):49–57. Epub 1999/02/06.
51. Lotan Y, Svatek RS, Malats N. Screening for bladder cancer: a perspective. World J Urol. 2008;26(1):13–8. Epub 2007/11/22.
52. Lotan Y, Svatek RS, Sagalowsky AI. Should we screen for bladder cancer in a high-risk population? A cost per life-year saved analysis. Cancer. 2006;107(5):982–90. Epub 2006/07/25.

http://www.springer.com/978-1-4939-1880-5

Management of Bladder Cancer
A Comprehensive Text With Clinical Scenarios
Konety, B.R.; Chang, S.S. (Eds.)
2015, XX, 479 p. 74 illus., 68 illus. in color., Hardcover
ISBN: 978-1-4939-1880-5