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Screening Adults for Bladder Cancer: Update of the 2004 Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Background: Bladder cancer is one of the 10 most frequently diagnosed cancers. Screening could identify high-grade bladder cancer at earlier stages, when it may be more easily and effectively treated.

Purpose: To update the 2004 U.S. Preventive Services Task Force (USPSTF) evidence review on screening for bladder cancer in adults in primary care settings.

Data Sources: We searched Ovid MEDLINE from 2002 to December 2009, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials through the fourth quarter of 2009, and the CancerLit subsection of PubMed through March 2010 to identify relevant articles. We identified additional studies from citations in relevant articles, including the previous USPSTF review. Searches were limited to English-language studies.

Study Selection: We selected randomized trials and controlled observational studies that directly evaluated screening for bladder cancer in adults. To evaluate indirect evidence on screening, we also included studies on the diagnostic accuracy of screening tests for bladder cancer, and randomized trials and controlled observational studies that reported clinical outcomes associated with treatment compared to no treatment in patients with screen-detected or superficial bladder cancer.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis: No randomized trials or high-quality controlled observational studies evaluated clinical outcomes associated with screening compared to no screening, or treatment of screen-detected bladder cancer compared to no treatment. No study evaluated the sensitivity or specificity of tests for hematuria, urinary cytology, or urinary biomarkers for bladder cancer in asymptomatic persons without a prior history of bladder cancer. The positive predictive value of screening is <10 percent in asymptomatic persons, including higher-risk populations. No study evaluated harms associated with treatment for screen-detected bladder cancer compared to no treatment.

Limitations: High-quality evidence was not available for any of the key questions.

Conclusions: Additional research is needed to determine whether screening of adults for bladder cancer leads to better outcomes compared to no screening.

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CHAPTER 1. INTRODUCTION

Scope and Purpose

Bladder cancer is the fourth most commonly diagnosed cancer in men and the ninth most commonly diagnosed cancer in women in the United States.[1] Screening could identify bladder cancer at earlier stages, when it may be more easily and effectively treated. The U.S. Preventive Services Task Force (USPSTF) last reviewed the evidence on bladder cancer screening in 2004. The USPSTF commissioned an update of the evidence review in 2009 in order to update its recommendation on screening. Bladder cancer remains an important public health problem, with no improvements in incidence or associated mortality since 1975.[2] There is important uncertainty regarding bladder cancer screening, particularly in higher-risk patients. In addition, since the last USPSTF review, research on urinary biomarkers for diagnosis of bladder cancer has accumulated substantially. The purpose of this report is to systematically evaluate the current evidence on screening for bladder cancer.

Condition Definition

In the United States, over 90 percent of bladder cancers are transitional cell carcinomas, 5 percent are squamous cell carcinomas, and less than 2 percent are adenocarcinomas.[3-5] Bladder cancer is typically staged according to the American Joint Committee on Cancer Tumor Node Metastases (TNM) criteria, in which the tumor stage (T) is based on the extent of penetration or invasion into the bladder wall and adjacent structures (**Table 1**).[6, 7] Superficial bladder cancers, or those that have not invaded the bladder smooth muscle, include stages Ta (noninvasive papillary carcinoma), Tis (carcinoma in situ), and T1 (tumor has invaded the subepithelial connective tissue) tumors. Tumors stage 2 and higher are muscle invasive. The likelihood of progression to invasive cancer is associated with the presence of more poorly differentiated cells and other histopathologic features. According to a 1998 World Health Organization and International Society of Urological Pathology consensus statement, transitional cell carcinomas are classified histopathologically into one of four categories: papilloma, papillary urothelial neoplasm of low malignant potential, low grade carcinoma, and high grade carcinoma.[8]

Prevalence and Burden of Disease

The incidence of bladder cancer in the United States in 2005 was approximately 21 per 100,000 persons, or 0.02 percent.[9] The American Cancer Society estimates that 70,980 new cases of bladder cancer will be diagnosed in the United States during 2009 (about 52,810 men and 18,170 women), and about 14,330 people will die of the disease (about 10,180 men and 4,150 women).[1] By comparison, it is estimated that there will be 219,440 new cases of lung cancer and 159,390 deaths (88,900 in men and 70,490 in women), 146,970 new cases of colorectal cancer and 49,920 deaths (25,240 in men and 24,680 in women), 42,470 new cases of pancreatic cancer and 35,240 deaths (18,030 in men and 17,210 in women), 192,280 new cases of prostate cancer and 27,360 prostate cancer deaths, 192,370 new cases of breast cancer and 40,170 breast cancer deaths, 42,160 new cases of uterine cancer and 7,780 uterine cancer deaths, and 11,270 new cases of cervical cancer

and 4,070 cervical cancer deaths. Bladder cancer occurs primarily in men older than 60 years of age and roughly twice as frequently in white compared to black men.[9]

Etiology and Natural History

Bladder cancer is a heterogeneous condition. Approximately 75 percent of newly diagnosed transitional cell carcinomas present as superficial tumors which can be treated with local (bladder-sparing) resection and intravesical therapy.[3] About 25 percent of newly diagnosed bladder cancer presents as invasive tumor.[10] Once bladder cancer invades muscle, it can quickly progress and metastasize, is associated with a poor prognosis, and its treatment may involve removal of the bladder or systemic chemotherapy. As many as 50–70 percent of superficial tumors will recur after initial treatment, with a 10–20 percent risk of progression to invasive tumor.[3] A major challenge for screening is to accurately identify tumors that are still superficial, yet at high risk for progression, in order to initiate interventions at a more treatable stage. Factors that influence risk of progression include the tumor stage and grade; the number, size, and appearance of lesions; the response to initial treatment; and other factors.

Risk Factors

Cigarette smokers are 2 to 4 times more likely to develop bladder cancer than nonsmokers.[11] Occupational exposures to carcinogens, particularly in the rubber, chemical, and leather industries, are also associated with increased risk for bladder cancer. For example, β-napthylamine (BNA), one of the best established carcinogens, is associated with a 200-fold increased risk of bladder cancer.[11] Other risk factors for bladder cancer include male sex, older age, white race, infections caused by certain bladder parasites, and having a family or prior personal history of bladder cancer.[11-14]

Rationale for Screening/Screening Strategies

The rationale for screening is that screening could identify high-grade superficial bladder cancer at earlier asymptomatic stages, when there is a greater chance of cure with bladder-sparing therapies.[15] Circumstances that would favor screening include the presence of a prolonged asymptomatic phase in which superficial bladder cancers at high risk for progression can be detected, availability of accurate screening tests, and availability of effective and safe treatments for bladder cancers detected by screening.

Interventions/Treatment

Once bladder cancer has been diagnosed, a number of factors affect prognosis and treatment options. These include the stage of the cancer (superficial versus invasive), tumor grade, whether the tumor is recurrent, the patient's age and general health, and other factors. The main treatment for superficial bladder cancer is local (bladder-sparing) resection (transurethral resection of bladder tumor or TURBT), often with adjuvant radiation therapy, intravesical chemotherapy, immunotherapy, or photodynamic therapy.[16] For invasive bladder cancer that is surgically

resectable, the main treatment is radical cystectomy, often with adjuvant or neoadjuvant systemic chemotherapy.

Current Clinical Practice

Screening tests that are feasible for primary care include the urine dipstick or microscopic urinalysis to detect hematuria (blood in the urine) and urine cytology to detect abnormal or cancerous cells in the urine. Urine biomarkers for bladder cancer, such as the nuclear matrix protein-22 (NMP22) complement factor H-related protein, would also be feasible for screening, but have not yet been widely adopted in primary care. One factor that could affect how urine biomarkers are used for screening is their cost, which varies substantially for different tests. Screening strategies could include testing all asymptomatic persons or targeted screening of high-risk groups based on smoking status, demographics, workplace exposures, or other factors. Patients with a positive screening test in primary care settings are referred to a urologist for further evaluation, which typically includes cystoscopy (with biopsy if a bladder tumor is found), and may include imaging and other studies.

Recommendations of Other Groups

No organization recommends routine screening for bladder cancer in asymptomatic older adults, including the American Cancer Society, the United Kingdom National Screening Committee, and the Canadian Task Force on Preventive Health Care.[6, 17, 18]

Previous USPSTF Recommendation

In 2004, the USPSTF recommended against routine screening for bladder cancer in adults (D recommendation). The USPSTF found fair evidence that screening can detect bladder cancer in asymptomatic individuals, but concluded that the potential benefit of screening would be small at best because many of the cancers detected by screening have a low tendency to progress to invasive disease, there is a relatively low overall prevalence of asymptomatic bladder cancer that would eventually lead to important clinical consequences, and because of insufficient evidence that early treatment of bladder cancer detected through screening improves long-term health outcomes. The potential harms of screening were assessed as at least small, based on the low positive predictive value of screening tests (resulting in many false-positive test results), which could lead to unnecessary invasive procedures (such as cystoscopies and biopsies) or other tests. As a result, the USPSTF concluded that the potential harms of screening for bladder cancer outweigh potential benefits.

CHAPTER 2. METHODS

Key Questions and Analytic Framework

Using the methods of the USPSTF that are fully described in the Appendix and with the input of members of the USPSTF, we developed an analytic framework (**Figure 1**) and Key Questions to guide our literature search and review.

The Key Questions used to guide this evidence synthesis are:

1. Is there direct evidence that screening for bladder cancer reduces morbidity or mortality?
2. What are the accuracy and reliability of urinalysis for hematuria, urine cytology, and urine biomarkers for identification of bladder cancer?
3. Does treatment of screen-detected bladder cancer reduce morbidity and mortality from this disease?
4. What are the harms of screening for bladder cancer and treatment of screen-detected bladder cancer?

Search Strategies

We searched Ovid MEDLINE from 2002 to December 2009, the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials through the fourth quarter of 2009, and the CancerLit subsection of PubMed through March 2010 to identify relevant articles (**Appendix 1**). We identified additional studies from reference lists of relevant articles, including the previous USPSTF review.

Study Selection

We selected studies pertaining to screening, diagnosis, and treatment of bladder cancer based on pre-defined inclusion and exclusion criteria (**Appendix 2**). Two reviewers evaluated each study at the title/abstract and full-text article stages to determine eligibility for inclusion. The flow of studies from initial identification of titles and abstracts to final inclusion or exclusion is diagrammed in **Appendix 3**. We defined the target population as asymptomatic persons older than 50 years of age. Our focus was studies performed in primary care settings, but we also included studies conducted in occupational settings. We excluded studies that enrolled patients with recurrent bladder cancer. We also excluded studies that enrolled patients with gross hematuria, dysuria, or other signs or symptoms associated with bladder cancer, as these were considered symptomatic and therefore outside the scope of screening. Studies that enrolled a mixed population of asymptomatic and symptomatic individuals were included if results were reported separately for asymptomatic patients without previous bladder cancer, or if >85 percent of enrollees satisfied these criteria. Outcomes of interest were morbidity and mortality and adverse events related to screening or treatment, and measures of diagnostic accuracy for screening tests.

We included randomized, controlled trials and controlled observational studies (cohort and case-

control studies) that directly assessed effects of bladder cancer screening compared to not screening on morbidity, mortality, or harms. We also included studies that evaluated the diagnostic accuracy of urinalysis for hematuria, cytology, and urinary biomarkers compared to results of cystoscopy. For treatment, we focused on randomized, controlled trials and controlled observational studies comparing benefits and harms of TURBT and/or intravesical therapy compared to no treatment for screen-detected or superficial bladder cancer (the type most likely to be detected by screening and amenable to early treatment). We restricted our review to published studies available in the English language. Studies that were excluded after review of the full-text articles and reasons for exclusion are listed in **Appendix 4**.

Data Abstraction and Quality Rating

We abstracted details about the patient population, study design, data analysis, follow-up, and results. One author abstracted data and another author verified data abstraction for accuracy. We used predefined criteria developed by the USPSTF to assess the risk of bias (quality) of studies (**Appendix 5**).[19, 20] For randomized trials, we assessed methods of randomization, allocation concealment, and blinding; loss to follow-up; and use of intention-to-treat analysis. Two authors independently rated the internal validity of each study as "good," "fair," or "poor" based on the number and seriousness of methodological shortcomings. When data were available from diagnostic accuracy studies, we used the *diagti* procedure in Stata (Stata version 10, StataCorp, College Station, TX) to calculate sensitivities, specificities, and likelihood ratios. For all studies, we evaluated applicability to populations likely to be encountered in primary care screening settings, based on whether patients were recruited from primary care or community settings, the proportion of patients with signs or symptoms suggesting bladder cancer, occupational exposures, the stage of bladder cancer, and the proportion of patients with a previous bladder cancer diagnosis. Discrepancies in quality ratings were resolved by discussion and consensus.

Data Synthesis

We assessed the overall strength of the body of evidence for each Key Question ("good," "fair," or "poor"), or part of a Key Question, using methods developed by the USPSTF, based on the number, quality, and size of studies, consistency of results between studies, and directness of evidence.[19] Because few studies met inclusion criteria, we did not quantitatively pool results.

External Review

We distributed a draft of the report for review by external experts not affiliated with the USPSTF (**Appendix 6**), and revised the report based on their comments.

CHAPTER 3. RESULTS

Key Question 1. Is there direct evidence that screening for bladder cancer reduces morbidity or mortality?

Summary

We identified no randomized, controlled trials of screening for bladder cancer. Three observational studies found screening for bladder cancer associated with decreased risk of bladder cancer mortality or lower stage at diagnosis (or trends toward decreased risks), but were difficult to interpret due to important methodological shortcomings.[21-23]

Evidence

We identified no randomized, controlled trials of screening for bladder cancer. One older prospective study[24] was included in the previous USPSTF report, with results reported for up to 8.5 years of follow-up (**Table 2**). For this update, we included results through 14 years of follow-up. The study evaluated screening in community-dwelling men ages 50 or older (n=1,575), with a comparison group consisting of patients newly diagnosed with bladder cancer and entered in a statewide registry (n=511). About half of the men invited to participate in the study declined. Screening was based on repeated urine self-testing at home for up to 1 year. 16 percent (258/1575) of screened men had hematuria, and 1.3 percent (21/1575) were diagnosed with bladder cancer, including one case of muscle-invasive cancer (0.06 percent). The proportion of bladder cancers that were classified as low-grade and superficial at the time of diagnosis was similar in the screen-detected and cancer registry groups (52 percent vs. 57 percent; relative risk [RR], 0.92 [95% confidence interval, 0.61–1.4]). The proportion of high-grade, superficial bladder cancers was higher in the screened group (43 percent vs. 19 percent; RR, 2.2 [95% CI, 1.3–3.7]), with a non-statistically significant trend toward a decreased proportion of invasive bladder cancers (5 percent vs. 24 percent; RR, 0.20 [95% CI, 0.03–1.4]). After 14 years of follow-up, the risk of bladder cancer death was lower in the screened group compared to the cancer registry patients (0 percent or 0/21 vs. 20 percent or 104/509; p=0.01), primarily due to a decrease in risk in patients with high-grade or invasive cancers (0 percent or 0/10 vs. 38 percent or 77/200; p=0.01).[22] Largely due to the effects on bladder cancer-related mortality, the risk of all-cause mortality was also lower in the screened group (43 percent or 9/21 vs. 74 percent or 377/509; RR, 0.58 [95% CI, 0.35–0.95]). We rated this study as poor quality because it did not assemble an inception cohort of comparable unscreened subjects. Results are highly susceptible to confounding due to differences between the screened patients and those entered in the registry, lead-time bias, length-time bias, sparse data (due to no deaths in the screened group), and other factors. No attempt was made to adjust or control for potential confounders. The study reported bladder cancer rates among the cohort of men invited to enroll in the screening study but who declined (based on cases reported to the statewide registry). Rates of new bladder cancers were identical among screened patients and those who did not participate in the study (1.3 percent vs. 1.2 percent), but clinical outcomes were not compared.
We identified two other poor-quality studies that met inclusion criteria and were not included in the prior evidence review (**Table 2**).[21, 23] A cohort study found that in aluminum production workers

exposed to benzene-soluble coal-tar-pitch volatile chemicals, there were non-statistically significant trends toward a higher proportion of early-stage bladder cancer at diagnosis (77 percent vs. 67 percent) and increased 5-year survival (RR, 0.54 [95% CI, 0.20–1.48]) after annual urine cytology screening was instituted compared to before the screening program.[23] This study was rated poor quality because it evaluated a historical control group and did not attempt to adjust or control for confounders. A case-control study found that persons who died from bladder cancer had lower odds of having received a screening urinalysis in the previous 5 years, after adjustment for smoking status and occupational bladder cancer exposure (odds ratio [OR], 0.60 [95% CI, 0.41–0.87).[21] This study was rated poor quality because it could not accurately ascertain the reason that urinalyses were obtained.

Other prospective studies on bladder cancer screening did not meet inclusion criteria because they were uncontrolled, but may provide some information regarding the yield of screening in different populations. Two European studies of older (>60 years), average-risk men screened with urine dipstick for hematuria found bladder cancer in 0.5 percent (5/1096)[25] and 0.7 percent (17/2356) of subjects.[26] A study of higher-risk men and women with ≥40 packs/year smoking history found that 3.3 percent (6/183) had bladder cancer identified following one-time screening with a battery of tests (urine dipstick, NMP22, and cytology).[27] A study of higher-risk men and women with >10-year history of smoking or >15-year history of a high-risk occupation found 0.2 percent (3/1502) had bladder cancer following one-time screening with a test for NMP22.[28] One study that periodically screened workers with occupational exposures to BNA or benzidine with urinalysis, cytology, and/or urine biomarkers identified bladder cancer in 1.0 percent (3/304) of subjects.[29]

Key Question 2. What are the accuracy and reliability of urinalysis for hematuria, urine cytology, and urine biomarkers for identification of bladder cancer?

Summary

No study evaluated the diagnostic accuracy of screening tests for bladder cancer in asymptomatic persons without a prior history of bladder cancer. A subgroup analysis from one study of patients without gross hematuria reported a sensitivity of 0.45, specificity of 0.86, and positive predictive value of 0.11 (bladder cancer prevalence 4 percent), but included patients with dysuria.[30] Positive predictive values were less than 10 percent in screening studies of asymptomatic persons, including high-risk populations.

Evidence

No study evaluated the diagnostic accuracy of screening tests for bladder cancer in asymptomatic persons. All studies, even those that did not focus on patients with previously diagnosed bladder cancer,[31-33] enrolled patients with gross hematuria and/or urinary symptoms such as dysuria, typically in referral settings. Only one study provided data to calculate the diagnostic accuracy of NMP22 compared to cystoscopy in a subgroup of patients without gross hematuria (with or without dysuria).[30] The study reported a sensitivity of 0.45 (17/38 [95% CI, 0.29–0.62]) and specificity of 0.86 (889/1028 [95% CI, 0.84–0.88]) for a positive likelihood ratio of 3.3 (95% CI, 2.2–4.9) and

negative likelihood ratio of 0.64 (95% CI, 0.48–0.85). The positive predictive value was 0.11 (17/156 [95% CI, 0.07–0.17), with a bladder cancer prevalence of 4 percent (38/1066 [95% CI, 3–5]). By comparison, the positive predictive value in patients with gross hematuria (bladder cancer prevalence 18 percent) was 0.43 (26/61).

Six studies reported positive predictive values in screened asymptomatic patients, but did not meet inclusion criteria because other markers of diagnostic accuracy could not be calculated, since patients with negative screening tests did not undergo cystoscopy.[24, 25, 27-29, 34] The positive predictive value of screening (one-time testing for hematuria or NMP22) ranged from 3 percent to 5 percent in three studies[25, 28, 34] in which the bladder cancer prevalence was <1 percent, including one study that enrolled higher-risk patients based on smoking and occupational history.[28] The positive predictive value was 8 percent in three studies with a prevalence ranging from 1 percent to 3 percent, based on screening with repeated urinalysis or one-time screening with multiple tests (urinalysis, cytology, and urine biomarkers),[24, 27, 29] including one study of people with high-risk occupational exposures.[29]

Key Question 3. Does treatment of screen-detected bladder cancer reduce morbidity and mortality from this disease?

We identified no randomized trials or controlled observational studies of treatment for screen-detected or superficial bladder cancer compared to no treatment.

Key Question 4. What are the harms of screening for bladder cancer or treatment of screen-detected bladder cancer?

Summary

We identified no randomized, controlled trials or controlled observational studies on harms of treatment compared to no treatment. In one large uncontrolled observational study, bleeding and perforation occurred in 2.8 percent and 1.3 percent of patients treated with TURBT, respectively.[35]

Evidence

Potential harms of screening for bladder cancer can occur in the evaluation of positive tests or with subsequent treatments. Follow-up of positive screenings typically includes cystoscopy and may include imaging studies. Potential harms include anxiety, labeling, discomfort or pain related to cystoscopy, and complications related to cystoscopy and biopsy (such as perforation, bleeding, or infection) and imaging (such as effects related to use of intravenous contrast or radiation exposure).[36-39] Screening could also increase the overall exposure to additional procedures and treatments due to earlier initiation of routine surveillance and frequent recurrences of tumor.

We identified no controlled studies that directly measured harms associated with screening for bladder cancer. Compared to higher-prevalence populations, lower-prevalence populations would be exposed to a greater potential for unnecessary harms due to higher false-positive rates of

screening (see Key Question 2). However, we identified no studies estimating the magnitude of harms associated with unnecessary procedures.

We also identified no controlled studies comparing harms of treatment of screen-detected bladder cancer versus no treatment. Although one large (n=2,821) uncontrolled observational study reported rates of bleeding (2.8 percent) and perforation (1.3 percent) with TURBT, it isn't possible to estimate the incremental harms that may have occurred due to screening from this data.[35] In this study, the presence of larger (>3 cm) or more (≥3) tumors increased the risk of complications. Higher tumor stage did not correlate with increased risk.

CHAPTER 4. DISCUSSION

Summary of Review Findings

Table 3 summarizes the results of this evidence synthesis by Key Question. Bladder cancer is one of the 10 most frequently diagnosed cancers in the United States, but evidence on the natural history of asymptomatic bladder cancer is lacking, since tumors are typically treated following diagnosis.[16] In addition, the variability in the natural history of bladder cancer with respect to risk of tumor progression from superficial to muscle invasive or metastatic bladder cancer and the relatively low incidence of bladder cancer mortality relative to the incidence of new cases present challenges in evaluating potential benefits and harms of screening.[3, 16] Major gaps in the evidence make it impossible to reach any reliable conclusions about screening. We identified no high-quality randomized, controlled trials or controlled observational studies showing that bladder cancer screening is associated with improved clinical outcomes compared to no screening. The only controlled cohort studies on screening suggest that screening might result in a shift to earlier stage bladder cancer diagnoses or reduce the long-term risk of bladder cancer-related mortality, but the studies had serious methodological shortcomings, including selection of noncomparable control groups and failure to adjust for potential confounders.[23, 24]

In terms of indirect evidence, we could not estimate the effectiveness of treatments for screen-detected bladder cancer, as there are no studies comparing clinical outcomes associated with treatment versus no treatment. Evidence on the diagnostic accuracy of screening tests in asymptomatic patients with a prior history of bladder cancer is limited to studies reporting positive predictive values, without data on sensitivity or specificity. A number of recent studies have evaluated urine biomarkers, but their main focus has been on diagnostic accuracy for recurrent bladder cancer or in patients with gross hematuria or lower urinary tract symptoms, rather than in asymptomatic persons relevant for screening. In screening studies of asymptomatic persons, the positive predictive value is less than 10 percent, even in higher-risk populations, which could result in unnecessary procedures and associated harms, including bleeding and perforation.[25, 27-29, 34] However, there are no reliable data to estimate the magnitude of harms associated with screening for bladder cancer compared to no screening or the magnitude of harms associated with treatment of screen-detected bladder cancer versus no treatment.

Limitations

The major limitation of this review is the lack of evidence addressing any of the Key Questions.

Emerging Issues/Next Steps

We identified no ongoing or planned trials of screening compared to no screening. A number of newer urinary biomarkers for bladder cancer are under investigation,[40, 41] but have not been evaluated for their usefulness in screening.

Future Research

Randomized trials or appropriately designed cohort studies that compare results of screening compared to no screening on clinical outcomes are needed to understand the effects of screening compared to no screening on clinical outcomes. Screening strategies to be evaluated could include testing all asymptomatic persons or targeted screening of high-risk groups based on smoking status, demographics, workplace exposures, or other factors, in order to help define optimal screening strategies. It would be appropriate to focus initial randomized trials on higher-risk groups, as the greater incidence of bladder cancer could result in a higher yield from screening and allow researchers to enroll smaller sample sizes. If randomized trials show benefit in high-risk groups, future trials could evaluate testing of all asymptomatic persons. In lieu of randomized trials, cohort studies could be helpful for understanding risks and benefits of screening, but to be more informative than currently available studies, they should be designed with appropriate attention to potential confounding and selection of appropriate control groups. If screening is shown to be effective, studies should evaluate the comparative diagnostic accuracy of urine tests for hematuria, urinary cytology, and urinary biomarkers in asymptomatic patients, in order to better inform the selection of screening tests. Randomized trials of treatment compared to no treatment for screen-detected or superficial bladder cancer could be difficult to implement, as TURBT has become the standard of care in any case where bladder cancer is either suspected or confirmed.[42] Therefore, it may be more feasible—and provide more direct evidence—to focus future research efforts on trials of screening compared to no screening, rather than to attempt trials of treatment versus no treatment.

Conclusions

Additional research is needed to determine whether screening of adults leads to better outcomes than no screening.

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31. Grossman HB, Messing E, Soloway M, et al. Detection of bladder cancer using a point-of-care proteomic assay. *JAMA.* 2005;293(7):810-816.
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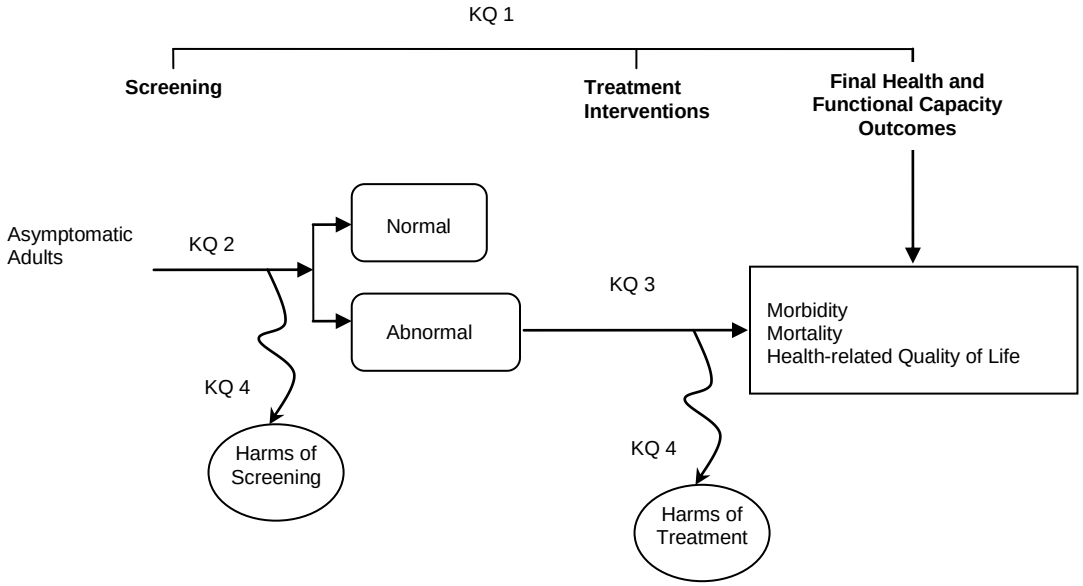
Figure 1. Analytic Framework and Key Questions



Key Question 1. Is there direct evidence that screening for bladder cancer reduces morbidity or mortality?

Key Question 2. What are the accuracy and reliability of urinalysis, urinary cytology, and other urinary biomarkers for identification of bladder cancer?

Key Question 3. Does treatment of screen-detected bladder cancer reduce morbidity and mortality from this disease?

Key Question 4. What are the harms of screening for bladder cancer and treatment of screen-detected bladder cancer?

Abbreviation: KQ = key question.

Table 1. Bladder Cancer Tumor Staging

TX	Primary tumor cannot be assessed
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ
T1	Tumor invades lamina propria
T2	Tumor invades muscularis propria T2a: Invades superficial muscularis propria (inner half) T2b: Invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue/fat T3a: Invades perivesical tissue/fat microscopically T3b: Invades perivesical tissue/fat macroscopically (extravesical mass)
T4	Tumor invades prostate, uterus, vagina, pelvic wall, or abdominal wall T4a: Invades adjacent organs (uterus, ovaries, prostate stoma) T4b: Invades pelvic wall and/or abdominal wall

Sources: American Urological Association, 2007[42] and Greene et al, 2002[43]

Table 2. Screening Studies

Study, Year, Title	Population and country	Study design	Screening test	Sample size	Results	Quality Score
Friedman et al, 1995[21]	Cases: Fatal bladder cancer among Kaiser Permanente subscribers Controls: Alive and a member of Kaiser Permanente, matched on age, sex, and date of joining program	Case-control study	Urinalysis	290 cases and 290 controls	**Bladder cancer death vs. live matched controls** Screening urinalysis within the 5 years prior to symptoms or findings leading to the cancer diagnosis (adjusted for smoking and occupational bladder cancer risk): OR, 0.60 (95% CI, 0.41–0.87) Any urinalysis within the 5 years prior to symptoms or findings leading to the cancer diagnosis (adjusted for smoking and occupational bladder cancer risk): OR, 0.94 (95% CI, 0.61–1.46)	**Poor**. Unable to accurately ascertain reason for urinalyses or presence of symptoms
Messing et al, 1995[24] Other publications: Messing et al, 2006[22]	Asymptomatic men >50 years old from primary care settings (screening population) and bladder cancer cases reported to a statewide registry; United States	Prospective cohort of screened subjects compared to cases reported to a statewide registry	Periodic home urinalysis for hematuria	1,575 in screening cohort (1,940 declined to participate), 511 cases reported to cancer registry	Rate of positive screens:16% (258/1574) Positive predictive value: 8% (21/258) **Screened patients vs. registry cases** Low-grade superficial bladder cancer at diagnosis: 52% (11/21) vs. 57% (290/511); RR, 0.92 (95% CI, 0.61–1.4) High-grade superficial bladder cancer at diagnosis: 43% (9/21) vs. 99/511 (19%); RR, 2.2 (95% CI, 1.3–3.7) Muscle invasive or higher bladder cancer at diagnosis: 4.8% (1/21) vs. 24% (122/511); RR, 0.20 (95% CI, 0.03–1.4) Bladder cancer death at 14 years: 0% (0/21) vs. 20% (104/509); p=0.01 Overall mortality at 14 years: 43% (9/21) vs. 54% (273/509); RR, 0.80 (95% CI, 0.48–1.32) **Screened patients vs. unscreened patients** Bladder cancer diagnosis: 1.3% (21/1574) vs. 1.2% (23/1940)	**Poor**. No inception cohort of comparable unscreened subjects, no adjustment for potential confounders

Table 2. Screening Studies

Study, Year, Title	Population and country	Study design	Screening test	Sample size	Results	Quality Score
Theriault et al, 1990[23]	Aluminum workers with >5–10 years exposure to tar volatiles and diagnosed with bladder cancer when screening program in place (1980–1986) vs. prior to screening program (1970–1979); Quebec	Retrospective cohort study with historical control	Annual urine cytology	79 (30 screened and 49 not screened)	**Screened vs. not screened** Early-stage bladder cancer: 77% (23/30) vs. 67% (33/49); p>0.10 Mortality (age-adjusted): RR, 0.54 (95% CI, 0.20–1.48)	**Poor**. Historical cohort, no adjustment for potential confounders

Abbreviations: CI = confidence interval, RR = relative risk.

Table 3. Summary of Evidence

Number of studies *Overall quality rating*	Limitations	Consistency	Primary care applicability	Summary of findings
KQ 1. Is there direct evidence that screening for bladder cancer reduces morbidity or mortality?				
3 studies (4 publications) *Overall quality rating: poor*	3 poor-quality observational studies; no inception cohort of similar unscreened subjects, historical control, or inaccurate ascertainment of exposures and symptoms	No important inconsistency	Low to moderate	No randomized, controlled trials of screening for bladder cancer were identified. 3 observational studies found screening for bladder cancer associated with decreased risk of bladder cancer mortality or lower stage at diagnosis (or trends toward decreased risks), but were difficult to interpret due to important methodological shortcomings.
KQ2. What are the accuracy and reliability of urinalysis for hematuria, urine cytology, and urine biomarkers for identification of bladder cancer?				
No studies	All studies enrolled patients with previous bladder cancer or signs and symptoms of bladder cancer	No studies	No studies	No studies evaluated the sensitivity or specificity of diagnostic tests for bladder cancer in patients without previous bladder cancer or signs and symptoms associated with bladder cancer. 6 studies found a positive predictive value of <10% for screening in asymptomatic persons, including high-risk populations.*
KQ3. Does treatment of screen-detected bladder cancer reduce morbidity and mortality from this disease?				
No studies	No studies met inclusion criteria	No studies	No studies	No evidence; no randomized, controlled trials or controlled observational studies were identified.
KQ4. What are the harms of screening for bladder cancer or treatment of screen-detected bladder cancer?				
No studies	No studies met inclusion criteria	No studies	No studies	No randomized, controlled trials or controlled observational studies were identified. Harms of screening are likely to be related to the false-positive rate (see KQ2). One large uncontrolled observational study of transurethral resection of bladder tumor reported bleeding in 2.8% and perforation in 1.3%, with no associated mortality.

*These studies did not meet formal inclusion criteria because they provided incomplete diagnostic information.

Abbreviation: KQ = key question

Appendix 1. Search Strategies

Overall

Database: CancerLit Subsection of PubMed
Search Strategy:
1 bladder cancer.mp. or Urinary Bladder Neoplasms/
2 mass screening.mp. or Mass Screening/
3 1 and 2
4 limit 3 to cancer
5 from 4 keep 1-182

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
1 (bladder adj2 (cancer$ or malign$ or tumor$ or neoplas$ or carcino$ or adenocarcino$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 screen$.mp.
3 (routine$ adj3 (test$ or detect$ or find$ or diagno$)).mp.
4 2 or 3
5 1 and 4
6 (mortal$ or death$ or fatal$ or dead).mp.
7 morbid$.mp.
8 6 or 7
9 8 and 1
10 (accura$ or inaccura$ or reliab$ or unreliab$ or incorrect$ or (false$ adj3 (positiv$ or negativ$))).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11 (diagnos$ adj3 (mistak$ or error$ or erroneous$ or wrong$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
12 (differential$ adj2 diagnos$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
13 10 or 11 or 12
14 1 and 13
15 ((gene or genet$ or DNA) adj2 (test or tests or testing or tested)).mp.
16 biomarker$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
17 15 or 16
18 17 and 1
19 ((early or earli$ or time$) adj5 (detect$ or diagnos$ or discover$)).mp.
20 1 and 19
21 14 or 18 or 9 or 20 or 5
22 from 21 keep 1-143

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
1 (bladder adj2 (cancer$ or malign$ or tumor$ or neoplas$ or carcino$ or adenocarcino$)).mp. [mp=title, abstract, full text, keywords, caption text]
2 screen$.mp.
3 (routine$ adj3 (test$ or detect$ or find$ or diagno$)).mp.
4 2 or 3
5 1 and 4

6 (mortal$ or death$ or fatal$ or dead).mp.
7 morbid$.mp.
8 6 or 7
9 8 and 1
10 (accura$ or inaccura$ or reliab$ or unreliab$ or incorrect$ or (false$ adj3 (positiv$ or negativ$))).mp. [mp=title, abstract, full text, keywords, caption text]
11 (diagnos$ adj3 (mistak$ or error$ or erroneous$ or wrong$)).mp. [mp=title, abstract, full text, keywords, caption text]
12 (differential$ adj2 diagnos$).mp. [mp=title, abstract, full text, keywords, caption text]
13 10 or 11 or 12
14 1 and 13
15 ((gene or genet$ or DNA) adj2 (test or tests or testing or tested)).mp.
16 biomarker$.mp. [mp=title, abstract, full text, keywords, caption text]
17 15 or 16
18 17 and 1
19 ((early or earli$ or time$) adj5 (detect$ or diagnos$ or discover$)).mp.
20 1 and 19
21 14 or 18 or 9 or 20 or 5
22 from 21 keep 1-39

Screening
Database: Ovid MEDLINE
Search Strategy:
1 exp Urinary Bladder Neoplasms/
2 exp Mass Screening/
3 1 and 2
4 exp Urinary Bladder Neoplasms/pa, ri, us, di, ra, pc
5 screen$.mp.
6 4 and 5
7 6 or 3
8 exp Vital Statistics/
9 8 and 7
10 morbid$.mp.
11 (mortal$ or death$ or fatal$ or dead).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12 mo.fs.
13 11 or 10 or 12
14 7 and 13
15 9 or 14
16 (200$ not (2000$ or 2001$)).ed.
17 16 and 15
18 from 17 keep 1-48

Diagnostic Accuracy
Database: Ovid MEDLINE
Search Strategy:

1 exp Urinary Bladder Neoplasms/
2 exp Urinary Bladder Neoplasms/di
3 exp Urinary Bladder Neoplasms/ge
4 exp "Sensitivity and Specificity"/
5 3 or 2
6 4 and 5
7 (accura$ or inaccura$ or reliab$ or unreliab$ or incorrect$ or (false$ adj3 (positiv$ or negativ$))).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 5 and 7
9 exp Diagnostic Errors/
10 9 and 5
11 exp Diagnosis, Differential/
12 11 and 5
13 exp biomarkers/
14 5 and 13
15 exp mass screening/ or screen$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16 (routine$ adj3 (test$ or detect$ or find$ or diagno$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
17 15 or 16
18 6 or 8 or 10 or 12 or 14
19 17 and 18
20 (200$ not (2000$ or 2001$)).ed.
21 19 and 20
22 from 21 keep 1-115

Treatment
Database: Ovid MEDLINE
Search Strategy:
1 exp Urinary Bladder Neoplasms/th, rt, dh, su, dt [Therapy, Radiotherapy, Diet Therapy, Surgery, Drug Therapy]
2 ((early or earli$) adj5 (detect$ or diagnos$ or discover$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3 1 and 2
4 exp Time/
5 4 and 1
6 exp Prognosis/
7 exp "Outcome Assessment (Health Care)"/
8 6 or 7
9 8 and 5
10 exp neoplasm staging/
11 1 and 4 and 10
12 exp Vital Statistics/
13 morbid$.mp.
14 (mortal$ or death$ or fatal$ or dead).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

15 mo.fs.
16 13 or 15 or 12 or 14
17 16 and 5
18 9 or 11 or 17
19 3 or 18
20 from 19 keep 1-421

Appendix 2. Inclusion and Exclusion Criteria

Settings

Include:
Studies of screening performed in settings generalizable to primary care
Studies of diagnostic accuracy performed in specialty settings, if the screening test is generalizable to primary care

Exclude:
Specialty settings and countries with populations not similar to the United States

Populations

Include:
Adults, ages 50 and older

Exclude:
Prior bladder cancer
Gross hematuria
Urinary symptoms

Screening Tests

Include:
Screening tests used or available in primary care settings (urine dipstick or urinalysis for microscopic hematuria, urine cytology, and urine biomarkers for bladder cancer)

Exclude:
Cystoscopy (except as gold standard examination)

Interventions

Include:
Surgery
Radiation therapy
Chemotherapy
Biologic therapy (biotherapy, immunotherapy)
Photodynamic therapy

Outcomes

Include:
Morbidity
Mortality
Health-related quality of life

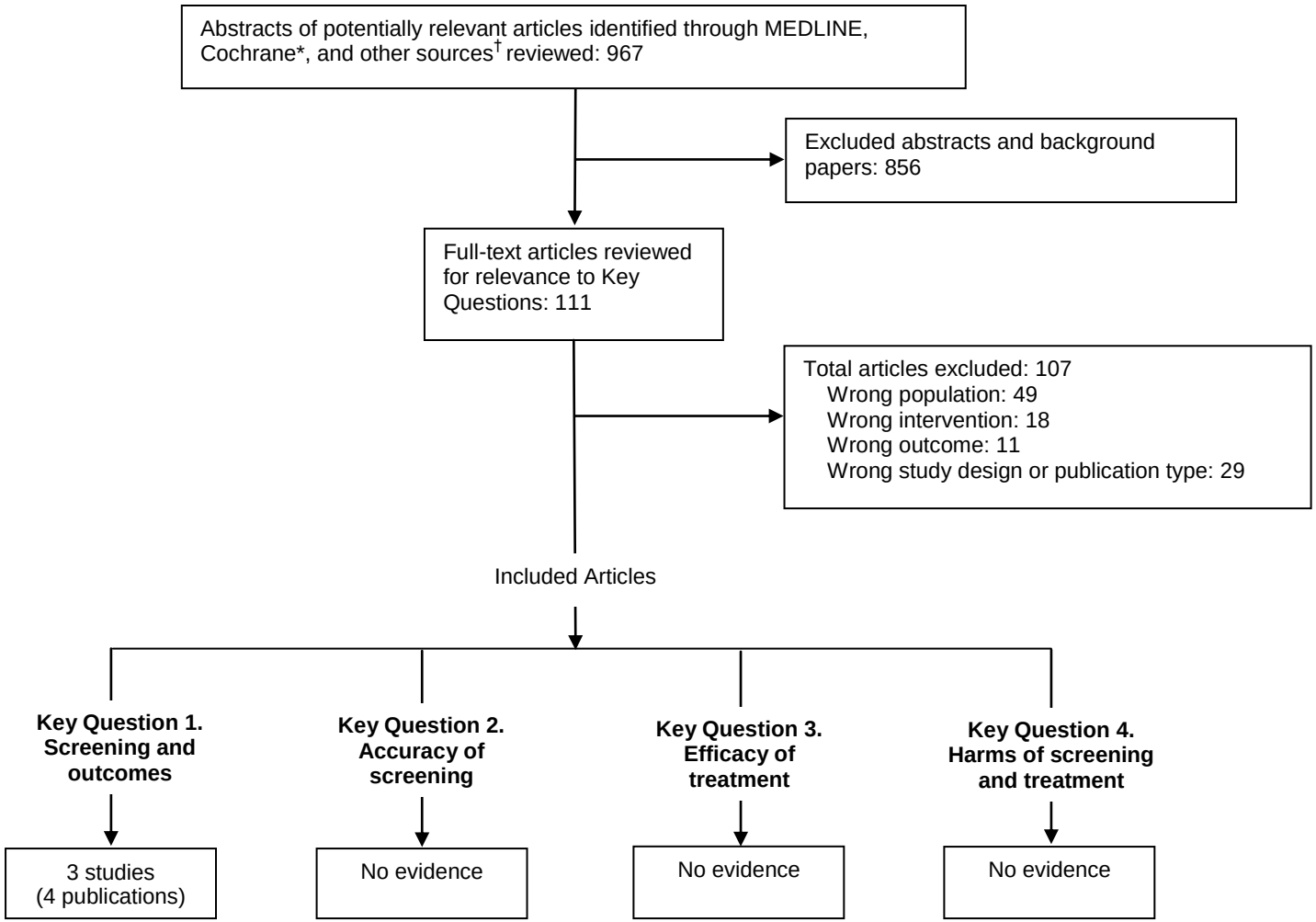
Study Types

Include:
Randomized, control trials of screening vs. no screening or treatment vs. no treatment
Cohort and case-control studies of screening vs. no screening or treatment vs. no treatment
High-quality systematic reviews

Studies of diagnostic accuracy in which the screening test is compared against a reference standard (cystoscopy)

Exclude:
Case series
Non-systematic reviews

Appendix 3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Other sources include reference lists, suggestions by experts, etc.

Wrong Population

Brake M, Loertzer H, Horsch R, et al. Long-term results of intravesical bacillus Calmette-Guerin therapy for stage T1 superficial bladder cancer. *Urology.* 2000;55(5):673-678.

Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: is cystectomy often too early? *J Urol.* 2001;165(3):808-810.

Britton J, Dowell A, Whelan P, et al. A community study of bladder cancer screening by the detection of occult urinary bleeding. *J Urol.* 1992;148:788-780.

Cai T, Bartoletti R. Long-term outcome of hematuria home screening for bladder cancer in men. *Cancer.* 2007;109(9):1923-1924.

Chahal R, Darshane A, Browning AJ, et al. Evaluation of the clinical value of urinary NMP22 as a marker in the screening and surveillance of transitional cell carcinoma of the urinary bladder. *Eur Urol.* 2001;40(4):415-420.

Chang YH, Wu CH, Lee YL, et al. Evaluation of nuclear matrix protein-22 as a clinical diagnostic marker for bladder cancer. *Urology.* 2004;64(4):687-692.

Cheng CW, Chan SFP, Chan LW, et al. Twelve-year follow up of a randomized prospective trial comparing bacillus Calmette-Guerin and epirubicin as adjuvant therapy in superficial bladder cancer. *Int J Urol.* 2005;12(5):449-455.

Cheng CW, Lau WK, Tan PH, et al. Cystoscopic diagnosis of bladder cancer by intravesical instillation of 5-aminolevulinic acid induced porphyrin fluorescence: the Singapore experience. *Ann Acad Med Singapore.* 2000;29(2):153-158.

Cookson MS, Herr HW, Zhang ZF, et al. The treated natural history of high risk superficial bladder cancer: 15-year outcome. *J Urol.* 1997;158(1):62-67.

Daniltchenko DI, Riedl CR, Sachs MD, et al. Long-term benefit of 5-aminolevulinic acid fluorescence assisted transurethral resection of superficial bladder cancer: 5-year results of a prospective randomized study. *J Urol.* 2005;174(6):2129-2133.

de Reijke TM, Kurth KH, Sylvester RJ, et al. Bacillus Calmette-Guerin versus epirubicin for primary, secondary or concurrent carcinoma in situ of the bladder: results of a European Organization for the Research and Treatment of Cancer—Genito-Urinary Group Phase III Trial. *J Urol.* 2005;173(2):405-409.

Di Stasi SM, Giannantoni A, Giurioli A, et al. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol.* 2006;7(1):43-51.

Duncan W, Arnott SJ, Jack WJ, et al. A report of a randomized trial of d(15)+Be neutrons compared with megavoltage X-ray therapy of bladder cancer. *Int J Radiat Oncol Biol Phys.* 1985;11(12):2043-2049.

Eissa S, Labib RA, Mourad MS, et al. Comparison of telomerase activity and matrix metalloproteinase-9 in voided urine and bladder wash samples as a useful diagnostic tool for bladder cancer. *Eur Urol.* 2003;44(6):687-694.

Eissa S, Swellam M, Ali-Labib R, et al. Detection of telomerase in urine by 3 methods: evaluation of diagnostic accuracy for bladder cancer. *J Urol.* 2007;178(3 Pt 1):1068-1072.

El-Ghobashy S, El-Leithy TR, Roshdy MM, et al. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term follow-up. *J Egypt Natl Canc Inst.* 2007;19(2):121-126.

Appendix 4. Excluded Studies

Fornari D, Steven K, Hansen AB, et al. Microsatellite analysis of urine sediment versus urine cytology for diagnosing transitional cell tumors of the urinary bladder. *APMIS.* 2004;112(2):148-152.

Friedrich MG, Pichlmeier U, Schwaibold H, et al. Long-term intravesical adjuvant chemotherapy further reduces recurrence rate compared with short-term intravesical chemotherapy and short-term therapy with Bacillus Calmette-Guérin (BCG) in patients with non-muscle-invasive bladder carcinoma. *Eur Urol.* 2007;52(4):1123-1130.

Gervino G, Autino E, Kolomoets E, et al. Diagnosis of bladder cancer at 465 MHz. *Electromagn Biol Med.* 2007;26(2):119-134.

Gore JL, Lai J, Setodji CM, et al. Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results–Medicare analysis. *Cancer.* 2009;115(5):988-996.

Green DF, Robinson MR, Glashan R, et al. Does intravesical chemotherapy prevent invasive bladder cancer? *J Urol.* 1984;131(1):33-35.

Grossman HB, Messing E, Soloway M, et al. Detection of bladder cancer using a point-of-care proteomic assay. *JAMA.* 2005;293(7):810-816.

Kageyama S, Isono T, Iwaki H, et al. Identification by proteomic analysis of calreticulin as a marker for bladder cancer and evaluation of the diagnostic accuracy of its detection in urine. *Clin Chem.* 2004;50(5):857-866.

Lahme S, Bichler KH, Feil G, et al. Comparison of cytology and nuclear matrix protein 22 (NMP 22) for the detection and follow-up of bladder-cancer. *Adv Exp Med Biol.* 2003;539 (Pt A):111-119.

Lam JS, Benson MC, O'Donnell MA, et al. Bacillus Calmete-Guerin plus interferon-alpha2B intravesical therapy maintains an extended treatment plan for superficial bladder cancer with minimal toxicity. *Urol Oncol.* 2003;21(5):354-360.

Lebret T, Bohin D, Kassardjian Z, et al. Recurrence, progression and success in stage Ta grade 3 bladder tumors treated with low dose bacillus Calmette-Guerin instillations. *J Urol.* 2000;163(1):63-67.

Lerner SP, Tangen CM, Sucharew H, et al. Patterns of recurrence and outcomes following induction bacillus Calmette-Guerin for high risk Ta, T1 bladder cancer. *J Urol.* 2007;177(5):1727-1731.

Leyh H, Hall R, Mazeman E, et al. Comparison of the Bard BTA test with voided urine and bladder wash cytology in the diagnosis and management of cancer of the bladder. *Urology.* 1997;50:49-53.

Leyh H, Marberger M, Conort P, et al. Comparison of the BTA stat test with voided urine cytology and bladder wash cytology in the diagnosis and monitoring of bladder cancer. *Eur Urol.* 1999;35(1):52-56.

Lotan Y, Capitanio U, Shariat SF, Hutterer GC, Karakiewicz PI. Impact of clinical factors, including a point-of-care nuclear matrix protein-22 assay and cytology, on bladder cancer detection. *Br J Urol.* 2009;103:1368-1374.

Luftenegger W, Ackermann DK, Futterlieb A, et al. Intravesical versus intravesical plus intradermal bacillus Calmette-Guerin: a prospective randomized study in patients with recurrent superficial bladder tumors. *J Urol.* 1996;155(2):483-487.

Madeb R, Messing EM. Long-term outcome of home dipstick testing for hematuria. *World J Urol.* 2008;26(1):19-24.

Messing EM, Young TB, Hunt VB, et al. Home screening for hematuria: results of a multi-clinic study. *J Urol.* 1992;148(2 pt 1):289-292.

Mian C, Pycha A, Wiener H, et al. Immunocyt 1: a new tool for detecting transitional cell cancer of the urinary tract. *J Urol.* 1999;161(5):1486-1489.

Miyanaga N, Akaza H, Tsukamoto T. Urinary nuclear matrix protein 22 as a new marker for the screening of urothelial cancer in patients with microscopic hematuria. *Int J Urol.* 1999;6(4):173–177.

Mutlu N, Turkeri L, Emerk K. Analytical and clinical evaluation of a new urinary tumor marker: bladder tumor fibronectin in diagnosis and follow-up of bladder cancer. *Clin Chem Lab Med.* 2003;41(8):1069-1074.

Parekattil SJ, Fisher HA, Kogan BA. Neural network using combined urine nuclear matrix protein-22, monocyte chemoattractant protein-1 and urinary intercellular adhesion molecule-1 to detect bladder cancer. *J Urol.* 2003;169(3):917-920.

Pfister C, Chautard D, Devonec M, et al. Immunocyt test improves the diagnostic accuracy of urinary cytology: results of a French multicenter study. *J Urol.* 2003;169(3):921-924.

Planz B, Synek C, Robben J, et al. Diagnostic accuracy of DNA image cytometry and urinary cytology with cells from voided urine in the detection of bladder cancer. *Urology.* 2000;56(5):782-786.

Ponsky LE, Sharma S, Pandrangi L, et al. Screening and monitoring for bladder cancer: refining the use of NMP22. *J Urol.* 2001;166(1):75-78.

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Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test
- Random or consecutive selection of patients[20]
- Screening cutoff pre-determined[20]
- All patients undergo the reference standard[20]

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test is assessed; has few or handles indeterminate results in a reasonable manner; includes a large number (>100) of broad-spectrum patients with and without disease; study attempts to enroll a random or consecutive sample of patients who meet inclusion criteria[20]; screening cutoffs are pre-stated.[20]

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients (i.e., applicable to most screening settings).

Poor: Has important limitations such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size of very narrow selected spectrum of patients.

Randomized, Controlled Trials (RCTs) and Cohort Studies

Criteria:

- Initial assembly of comparable groups: RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of ratings based on above criteria:

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (follow-up at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some, but not all, important outcomes are considered; and some, but not all, potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exist: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking the outcome assessment); and key confounders are given little or no attention.

Case Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80%; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80% or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50%, or inattention to confounding variables.

Sources: Harris et al, 2001[19] and Leeflang et al, 2008[20]

Appendix 6. Expert Reviewers of the Draft Report

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