Screening for Bladder Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force

Description: Update of the 2004 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for bladder cancer.

Methods: The USPSTF performed a targeted literature search for new evidence on the benefits and harms of screening, the accuracy of primary care–feasible screening tests, and the benefits and harms of treatment.

Recommendation: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for bladder cancer in asymptomatic adults (I statement).

www.annals.org

For author affiliation, see end of text.

The U.S. Preventive Services Task Force (USPSTF) makes recommendations about preventive care services for patients without recognized signs or symptoms of the target condition.

It bases its recommendations on a systematic review of the evidence of the benefits and harms and an assessment of the net benefit of the service.

The USPSTF recognizes that clinical or policy decisions involve more considerations than this body of evidence alone. Clinicians and policymakers should understand the evidence but individualize decision making to the specific patient or situation.

SUMMARY OF RECOMMENDATION AND EVIDENCE

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for bladder cancer in asymptomatic adults (I statement).

See the Clinical Considerations section for additional information and suggestions for practice regarding the I statement for screening.

See the Figure for a summary of the recommendation and suggestions for clinical practice.

Table 1 describes the USPSTF grades, and Table 2 describes the USPSTF classification of levels of certainty about net benefit. Both are also available at www.annals.org.

RATIONALE

Importance

Bladder cancer is the fourth most commonly diagnosed cancer in men and the ninth most commonly diagnosed cancer in women in the United States. It is the seventh-leading cause of solid cancer–related deaths. An estimated 70,980 new cases of bladder cancer were diagnosed in the United States during 2009 (52,810 cases in men and 18,170 cases in women), and approximately 14,330 people died of the disease (10,180 men and 4,150 women). More than 90% of all cases of bladder cancer are classified as transitional cell carcinomas. Most newly diagnosed transitional cell carcinomas present as superficial tumors. The stages of bladder cancer include superficial (Ta or T1) and muscle-invasive tumors. Many superficial tumors (50% to 70%) will recur after treatment, with a 10% to 20% risk for the tumor to progress to the invasive stage. One fourth of all cases of bladder cancer and 20% to 40% of all invasive tumors have already metastasized to the lymph nodes at the time of diagnosis. Invasive bladder cancer is associated with a poor prognosis.

Detection

The evidence is inadequate regarding the diagnostic accuracy of potential tests (urinalysis for microscopic hematuria, urine cytology, or tests for urine biomarkers) for identifying bladder cancer in asymptomatic persons with no history of bladder cancer.

Benefits of Detection and Early Intervention

The USPSTF found inadequate evidence that screening for bladder cancer or treatment of screen-detected blad-
der cancer leads to improved disease-specific or overall morbidity or mortality.

**Harms of Detection and Early Intervention**

Screening may yield false-positive results. False-positive results may lead to anxiety, labeling, pain, and additional complications that result from diagnostic cystoscopy and biopsy (such as bladder perforation, bleeding, and infection) or imaging. The USPSTF found inadequate evidence on the harms of screening for bladder cancer. Evidence on the harms associated with early treatment, which may occur more frequently with greater detection of cases of early-stage cancer, is also inadequate.

**USPSTF Assessment**

The USPSTF concludes that the evidence is insufficient to determine the balance of benefits and harms of screening for bladder cancer in asymptomatic adults.

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**CLINICAL CONSIDERATIONS**

**Patient Population Under Consideration**

This recommendation applies to asymptomatic adults. Although adults with mild lower urinary tract symptoms (such as urinary frequency, hesitancy, urgency, dysuria, or nocturia) are not strictly asymptomatic, these symptoms are quite common and are not believed to be associated with an increased risk for bladder cancer. The USPSTF considered it reasonable to include these persons in the population under consideration for screening. Adults with gross hematuria or acute changes in lower urinary tract symptoms are not included in this population.

**Screening Tests**

Primary care–feasible screening tests for bladder cancer include identifying hematuria with a urine dipstick or mi-

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**Table: Screening for Bladder Cancer**

<table>
<thead>
<tr>
<th>Population</th>
<th>Asymptomatic Adults</th>
</tr>
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<tbody>
<tr>
<td>Recommendation</td>
<td>No recommendation</td>
</tr>
<tr>
<td>Grade</td>
<td>I (Insufficient Evidence)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Assessment</th>
<th>Risk factors for bladder cancer include:</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• Smoking</td>
</tr>
<tr>
<td></td>
<td>• Occupational exposure to carcinogens (e.g., rubber, chemical, and leather industries)</td>
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<tr>
<td></td>
<td>• Male sex</td>
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<tr>
<td></td>
<td>• Older age</td>
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<tr>
<td></td>
<td>• White race</td>
</tr>
<tr>
<td></td>
<td>• Infections caused by certain bladder parasites</td>
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<td></td>
<td>• Family or personal history of bladder cancer</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening Tests</th>
<th>Screening tests for bladder cancer include:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Microscopic urinalysis for hematuria</td>
</tr>
<tr>
<td></td>
<td>• Urine cytology</td>
</tr>
<tr>
<td></td>
<td>• Urine biomarkers</td>
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</tbody>
</table>

| Interventions    | The principal treatment for superficial bladder cancer is transurethral resection of the bladder tumor, which may be combined with adjuvant radiation therapy, chemotherapy, biologic therapies, or photodynamic therapies. Radical cystectomy, often with adjuvant chemotherapy, is used in cases of surgically resectable invasive bladder cancer. |

| Balance of Harms and Benefits | There is inadequate evidence that treatment of screen-detected bladder cancer leads to improved morbidity or mortality. There is inadequate evidence on harms of screening for bladder cancer. |

<table>
<thead>
<tr>
<th>Suggestions for Practice</th>
<th>In deciding whether to screen for bladder cancer, clinicians should consider the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Potential preventable burden: Early detection of tumors with malignant potential could have an important effect on the mortality rate of bladder cancer.</td>
</tr>
<tr>
<td></td>
<td>• Potential harms: False-positive results may lead to anxiety and unneeded evaluations, harms from cystoscopy and biopsy, harms from labeling and unnecessary treatments, and overdagnosis.</td>
</tr>
<tr>
<td></td>
<td>• Current practice: Screening tests used in primary practice include microscopic urinalysis for hematuria and urine cytology; urine biomarkers are not commonly used in part because of cost. Patients with positive findings are typically referred to a urologist for further evaluation.</td>
</tr>
</tbody>
</table>

For a summary of the evidence systemically reviewed in making these recommendations, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.
croscopic urinalysis, urine cytology, and tests for urine biomarkers.

Treatment

Once bladder cancer has been diagnosed, several factors determine treatment, including tumor grade, cancer stage (superficial vs. invasive), whether the tumor is recurrent, the patient’s age and overall health status, and patient and physician preferences. The principal treatment for superficial (Ta or T1) bladder cancer is transurethral resection of the bladder tumor, which may be combined with adjuvant radiation therapy, intravesical chemotherapy, immunotherapy, or photodynamic therapies. Radical cystectomy, often with adjuvant or neoadjuvant systemic chemotherapy, is used in cases of surgically resectable invasive bladder cancer.

Suggestions for Practice Regarding the I Statement

In deciding whether to screen for bladder cancer, clinicians should consider the following.

Potential Preventable Burden

Bladder cancer is similar to many other types of cancer in that it is a heterogeneous condition. Approximately 70% of all cases of newly diagnosed transitional cell carcinomas present as superficial tumors (including in situ); some of these tumors may never progress to advanced disease. However, some cases of bladder cancer invade the muscle tissue, progress, and metastasize; treatment has limited efficacy in these cases. Early detection of tumors with malignant potential may have an important effect on the mortality rate of bladder cancer. One challenge of screening for bladder cancer is accurately identifying cases of early-stage cancer (subepithelial and in situ) with a high risk for progression. Another area of uncertainty is determining whether providing earlier, less toxic treatment (such as immunotherapy) with the intention of preventing symptomatic progression results in fewer overall harms to the patient than providing more toxic treatment (such as radical cystectomy) only to those patients who develop symptomatic or advanced tumors. Persons at increased risk for bladder cancer include those who work in the rubber, chemical, or leather industries, as well as those who smoke, are male, are older, or have a family or personal history of bladder cancer.

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**Table 1. What the USPSTF Grades Mean and Suggestions for Practice**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Suggestions for Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is substantial.</td>
<td>Offer/provide this service.</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.</td>
<td>Offer/provide this service.</td>
</tr>
<tr>
<td>C</td>
<td>The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is moderate or high certainty that the net benefit is small.</td>
<td>Offer/provide this service only if other considerations support offering or providing the service in an individual patient.</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.</td>
<td>Discourage the use of this service.</td>
</tr>
</tbody>
</table>

I statement The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

<table>
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<td>I</td>
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</tr>
</tbody>
</table>

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**Table 2. USPSTF Levels of Certainty Regarding Net Benefit**

<table>
<thead>
<tr>
<th>Level of Certainty*</th>
<th>Description</th>
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<tbody>
<tr>
<td>High</td>
<td>The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.</td>
</tr>
<tr>
<td>Moderate</td>
<td>The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.</td>
</tr>
<tr>
<td>Low</td>
<td>The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.</td>
</tr>
</tbody>
</table>

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* The USPSTF defines certainty as “likelihood that the USPSTF assessment of the net benefit of a preventive service is correct.” The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.
Potential Harms
False-positive test results may result in anxiety and unneeded evaluations, diagnostic-related harms from cystoscopy and biopsy, harms from labeling or unnecessary treatments (such as transurethral resection of a bladder tumor, intravesical chemotherapy, or biologic therapies), and overdiagnosis.

Current Practice
Screening tests feasible for use in primary care include urine dipstick or microscopic urinalysis for hematuria, urine cytology, and tests for urine biomarkers. Tests for urine biomarkers are not commonly used in primary care in part because of their cost, although this varies substantially. Patients with positive screening results are typically referred to a urologist for further evaluation, which may include cystoscopy (and biopsy if a tumor is found), imaging, and other studies.

Other Considerations
Research Needs and Gaps
Several gaps in the evidence led the USPSTF to issue an I statement. Addressing these research needs could potentially provide sufficient evidence for the USPSTF to issue future screening recommendations. Cohort studies are needed to evaluate the natural history of early-stage, untreated bladder cancer (particularly that detected by screening) to allow a greater understanding of the potential overdiagnosis and overtreatment associated with screen-detected bladder cancer. Studies that compare the diagnostic accuracy of urine screening tests in representative populations are needed, as well as studies that assess the effect of screening on the incidence of bladder cancer, tumor characteristics, and subsequent treatments. Randomized, controlled trials or well-designed case–control studies that evaluate clinical outcomes in screened versus unscreened populations, which would provide direct evidence on benefits and harms of screening, have highest priority. Targeting populations at increased risk for bladder cancer because of patient characteristics or occupational exposure may be preferred to enhance feasibility and maximize clinical relevance. A better understanding of the harms related to screening and treatment are required. Methods for evaluating these harms could include conducting observational studies based on patient registries or large pharmacoepidemiologic databases. As noted, prospective cohort studies are needed to more accurately identify cases of early-stage cancer (subepithelial and in situ) with a high risk for progression. Future research should also clarify the trade-offs of using less-toxic treatments earlier and more frequently, to prevent symptomatic progression, versus using treatments with greater toxicity, which are typically reserved for those patients who develop symptomatic or advanced tumors.

Discussion
Burden of Disease
The incidence of bladder cancer in the United States is approximately 21 cases per 100,000 persons or 0.02%. It is the seventh-leading cause of death due to solid cancer in the United States. In 2009, an estimated 70,980 new cases of bladder cancer were diagnosed, and approximately 14,350 people died of the disease. In comparison, in 2009 there were an estimated 219,440 new cases of lung cancer and 159,390 deaths, 146,970 new cases of colorectal cancer and 49,920 deaths, 192,280 new cases of prostate cancer and 27,360 deaths, and 11,270 new cases of cervical cancer and 4,070 deaths (1).

Bladder cancer is a heterogeneous condition with a variable natural history. It also has a relatively low mortality rate relative to the incidence of new cases. As a result, risk for overdiagnosis and overtreatment is a major issue in bladder cancer screening. Thus, it is important to identify superficial tumors that are at high risk for progression and target treatment at an earlier, more treatable stage in persons with such tumors, while minimizing unnecessary treatments in those unlikely to have disease-specific morbidity or mortality (1).

Persons at increased risk for bladder cancer include those who smoke or have occupational exposure to carcinogens, such as those who work in the rubber, chemical, or leather industries. Other risk factors for bladder cancer include male sex, older age, white race, infections caused by certain bladder parasites, and a family or personal history of bladder cancer (1).

Scope of Review
To update its 2004 recommendation on screening for bladder cancer in asymptomatic persons (2), the USPSTF reviewed the current state of the evidence and identified new evidence that addresses previously identified gaps. The USPSTF reviewed new evidence on the benefits and harms of screening, the accuracy of primary care–feasible screening tests, and the benefits and harms of treatment.

Accuracy of Screening Tests
Primary care–feasible screening tests for bladder cancer include urinalysis for hematuria, urinary cytology, and tests for other urine biomarkers. No evidence was found regarding the diagnostic accuracy of screening tests in asymptomatic persons (3).

Effectiveness of Detection and Treatment
The USPSTF found no direct evidence that bladder cancer screening is associated with improved health outcomes compared with no screening. The USPSTF could not evaluate the effectiveness of treatments for screen-detected bladder cancer because of a lack of studies that compare clinical outcomes associated with treatment versus no treatment (3).
Potential Harms of Detection and Treatment

The USPSTF found inadequate evidence on the harms associated with bladder cancer screening. In screening studies, the positive predictive value of various tests was less than 10%, which suggests a significant burden of unnecessary follow-up procedures and associated harms. However, the USPSTF found no reliable data with which to estimate the incremental harms associated with screening for bladder cancer compared with no screening, or the harms associated with treatment of screen-detected bladder cancer versus no treatment.

Potential harms of screening for bladder cancer include false-positive test results and unnecessary subsequent diagnostic procedures, as well as earlier initiation of routine surveillance. Follow-up of positive screening results 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) or imaging (such as adverse effects related to the use of intravenous contrast) (4–7).

In lower-prevalence populations, more patients are potentially exposed to unnecessary harms because of a higher rate of false-positive results than in higher-prevalence populations.

One large, uncontrolled observational study of 2821 patients (8) reported bleeding and perforation in 2.8% and 1.3%, respectively, of patients who underwent transurethral resection of a bladder tumor. However, the incremental harms that may have occurred because of screening cannot be estimated from the data. As noted, the risk for overdiagnosis and overtreatment is substantial because of the relatively low mortality rate. Thus, it is important to assess the harms related to overtreating screen-detected bladder cancer that is unlikely to progress to death or disability.

Estimate of Magnitude of Net Benefit

The USPSTF found inadequate evidence on the diagnostic accuracy of screening tests for bladder cancer. The USPSTF also found inadequate evidence on the effectiveness of treatment and the harms of screening or treatment. Therefore, the USPSTF concluded that the evidence on the benefits and harms of screening is lacking.

Response to Public Comments

A draft of this recommendation statement was posted for public comment on the USPSTF Web site from 30 November 2010 to 28 December 2010. Six comments were received from individuals or organizations. All comments were reviewed during the creation of this final document. Specifically, input from clinical specialists led to changes in the description of treatments. In general, the comments supported the USPSTF’s specified research agenda.

UPDATE OF PREVIOUS USPSTF RECOMMENDATION

In 2004, the USPSTF recommended against routine screening for bladder cancer in adults because the USPSTF concluded that the harms outweighed the benefits of screening (D recommendation) (2). In 2009, the USPSTF performed a targeted literature review and found insufficient evidence to assess the benefits and harms of screening for bladder cancer. In 2004, the USPSTF concluded that the harms outweighed the benefits; however, this time the USPSTF reviewed mortality statistics and other epidemiologic data that suggested heretofore undemonstrated benefits of screening. As a result, the USPSTF changed its recommendation from a D to an I statement (insufficient evidence).

RECOMMENDATIONS OF OTHERS

No major organization recommends screening for bladder cancer in asymptomatic adults. In 2011, the American Academy of Family Physicians endorsed the USPSTF recommendation (9); however, it is currently reviewing this recommendation. The European Association of Urology states that the best approach to primary prevention of muscle-invasive bladder cancer is to eliminate active and passive smoking (10). The American Cancer Society states that prompt attention to bladder symptoms is the best approach for finding bladder cancer in its earliest, most treatable stages in persons with no known risk factors (11).

From the U.S. Preventive Services Task Force, Rockville, Maryland.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-1530.

Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.uspreventiveservicestaskforce.org).

References


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Please refer questions to Mary Beth Schaeffer at mschaeffer@acponline.org.
APPENDIX: U.S. PREVENTIVE SERVICES TASK FORCE

Members of the U.S. Preventive Services Task Force† at the time this recommendation was finalized are Virginia A. Moyer, MD, MPH, Chair (Baylor College of Medicine, Houston, Texas); Michael L. LeFevre, MD, MSPH, Co-Vice Chair (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, Co-Vice Chair (Mount Sinai School of Medicine, New York, New York); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, California); Susan Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Glenn Flores, MD (University of Texas Southwestern, Dallas, Texas); Adelita Gonzales Cantu, RN, PhD (University of Texas Health Science Center, San Antonio, Texas); David C. Grossman, MD, MPH (Group Health Cooperative, Seattle, Washington); George Isham, MD, MS (HealthPartners, Minneapolis, Minnesota); Rosanne M. Leipzig, MD, PhD (Mount Sinai School of Medicine, New York, New York); Joy Melnikow, MD, MPH (University of California Davis Medical Center, Sacramento, California); Bernadette Melnyk, PhD, RN (Arizona State University College of Nursing and Healthcare Innovation, Phoenix, Arizona); Wanda Nicholson, MD, MPH (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Carolina Reyes, MD (University of Southern California, Los Angeles, California); J. Sanford Schwartz, MD (University of Pennsylvania Medical School and the Wharton School, Philadelphia, Pennsylvania); and Timothy Wilt, MD, MPH (University of Minnesota Department of Medicine and Minneapolis Veteran Affairs Medical Center, Minneapolis, Minnesota). Previous Task Force members who also made significant contributions to this recommendation are Thomas G. DeWitt, MD (Children’s Hospital Medical Center, Cincinnati, Ohio) and Diana B. Petitti, MD, MPH (Arizona State University, Phoenix, Arizona).

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/about.htm.