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Screening for urologic malignancies in primary care: Pros, cons, and recommendations

ABSTRACT

Interest in screening for urologic cancers has grown in recent years. This article considers the pros and cons of screening for four epidemiologically compelling urologic cancers: prostate, bladder, kidney, and testicular. Unfortunately, many of the urologic cancers do not meet the criteria for a successful cancer screening program—namely, high prevalence, availability of a sensitive and specific screening test, ability to detect clinically important cancers at an early stage, and cost-effectiveness. While age-based screening for prostate cancer should be offered to the general population after discussion of its benefits and risks, for the other three urologic malignancies the current consensus points more toward selective screening based on specific patient risk factors.

INTRODUCTION

The urologic cancers represent almost one quarter of all cancers in the human body and can be associated with substantial morbidity and mortality **(Table 1)**.[1] Prostate and bladder cancer are two of the most prevalent cancers among American men, and public awareness of these and other urologic cancers has increased greatly over the past decade. The importance of hematuria as a warning sign for cancer, specifically bladder and kidney cancer, is becoming more ingrained in the public consciousness. As a result of these developments, interest in screening for these malignancies has grown among patients and physicians alike.

There are several general prerequisites for a successful cancer screening program:

- A highly prevalent cancer
- Availability of a sensitive and specific screening test with acceptable morbidity
- Ability of the test to detect clinically important cancers at an early stage and thereby improve outcomes
- Cost-effectiveness.

This article will review the utility of screening for four of the most epidemiologically compelling urologic cancers—prostate, bladder, kidney, and testicular—in the primary care setting.

PROSTATE CANCER

Epidemiology

Prostate cancer is the most common noncutaneous malignancy in the United States; 232,000 new cases were estimated to have been diagnosed in 2006 **(Table 1)**.[1] It is the third-leading cause of cancer deaths among American men, responsible for an estimated 32,000 deaths annually.[1] American men have a 17% lifetime risk of being diagnosed with prostate cancer and a 3.4% risk of dying from this disease.[2] Compared with other racial groups, African Americans are at increased risk of developing prostate cancer, tend to develop it at an earlier age, and tend to have more advanced disease at the time of diagnosis.

Symptoms, presentation, and screening options

Since symptoms from prostate cancer usually do not develop until the disease is at an incurable stage, screening strategies cannot be symptom-based. Screening options, which consist of periodic serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE), are aimed at facilitating early diagnosis of prostate cancer, when it is still at a curable stage.

Rationale and evidence for screening

Current evidence in support of screening for prostate cancer comes largely from national cancer trends and population-based studies. The PSA test was introduced in 1989, and age-adjusted death rates from prostate cancer subsequently declined by 4% per year (17.6% overall) from 1994 to 1998.[3] Population-based regional screening programs in Tyrol, Austria, and Olmsted County, Minnesota, have also shown

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TABLE 1
US incidence and mortality rates for urologic cancers relative to other common malignancies*

Cancer	Incidence (annual)	Mortality (annual)	% Mortality
Prostate	232,000	32,000	14%
Breast*	211,000	40,000	19%
Lung*	173,000	163,000	94%
Colorectal*	145,000	54,000	37%
Bladder	63,000	12,000	20%
Kidney	30,000	12,000	40%
Testicular	8,000	330	4%

* The three most common nonurologic malignancies are included for comparison. Rates are estimates for 2006 based on Centers for Disease Control and Prevention data.[1]

TABLE 2
Comparative cost-effectiveness of screening for prostate cancer and breast cancer*

	Prostate cancer	Breast cancer
Age-adjusted deaths per 100,000 population	25.6	25.4
Mortality-to-incidence ratio	0.18	0.22
Sensitivity of screening test†	70%–80%	67.5%–80%
Positive predictive value of screening test†	30%–42%	9%–22%
Cost per quality-adjusted life-year gained from screening test†	$8,700–$145,000	$232,000

* Based on data from Wilson and Crawford.[2]

† Serum prostate-specific antigen (PSA) test for prostate cancer; mammography for breast cancer.

substantial declines in prostate cancer mortality relative to national trends.[4,5] American prostate cancer mortality rates continue to decline, and in 2006 prostate cancer was overtaken by colorectal cancer as the second-leading cause of male cancer deaths.[1] Although some of the overall mortality reductions can be attributed to improvements in therapy, it is well recognized that currently the only way to significantly reduce prostate cancer death is treatment of localized disease, which requires early detection.

The only published randomized, prospective study of prostate cancer screening, conducted among 46,193 men in Québec, Canada, reported a 69% reduction in prostate cancer mortality among the 8,137 men who were screened compared with the 38,056 men who were not.[6] This study has been heavily criticized, however, as its data were not analyzed according to the intention-to-screen statistical methodology.

Opportunistic screening is driven by the logic that prostate cancer can be cured only when it is pathologically confined to the prostate and its environs and that screening increases the detection of clinically localized disease. In large screening studies, clinically confined cancers are detected in 85% to 99% of cases compared with 50% to 60% for cancers that are not discovered by screening.[7,8] Prostate cancer that is pathologically confined to the prostate is reported in up to 70% of patients in screening studies, and long-term cancer control rates of 90% are reported when these cancers are treated with radical prostatectomy.[9]

In light of the above, a strong rationale can be made for prostate cancer screening, and careful review of the data suggests that screening for this cancer compares favorably with screening for breast cancer, which is generally well accepted. Compared with screening mammography for breast cancer, screening for prostate cancer with the PSA test has a higher positive predictive value and is also more cost-effective **(Table 2)**.[2]

In addition, screening with the PSA test is associated with minimal harm to the patient. Approximately 4% of screened men will undergo prostate biopsy during the course of screening; although the possible side effects of prostate biopsy include temporary pain, bleeding, and infection, hospital admission is required in only 0.3% to 0.5% of cases.[10]

Of course, the rationale for screening is based on the premise that prostate cancer–related morbidity and mortality will be improved as a result of early-stage treatment. Conclusive evidence on that score is now available, such as from a recent randomized trial demonstrating a 44% relative risk reduction in cancer-specific mortality with radical prostatectomy for early prostate cancer compared with watchful waiting.[11] However, conclusive evidence from randomized trials that prostate cancer screening reduces all-cause mortality is currently lacking. Two large ongoing screening studies should address this question: the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial, which is being conducted in the United States, and the European Randomized Study of Screening for Prostate Cancer (ERSPC). Their results are likely to be released in 2008.

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Arguments against screening

A potential drawbacks to prostate cancer screening is that it will lead to the diagnosis and treatment of a large number of small, indolent tumors that would otherwise remain clinically covert until the patient died from other causes. The majority of screening-detected cancers are graded as 6 or less on the Gleason classification system for prostate cancer (scores range from 2 [least aggressive] to 10 [most aggressive]), and only an estimated 10% of patients with these cancers will die of prostate cancer within 10 years without treatment.[12] Estimates from the ERSPC suggest that annual screening programs for men aged 55 to 67 years lead to overdetection (ie, detection of cancers that would not have been diagnosed in the absence of screening) in 56% of men diagnosed with prostate cancer.[13]

If these estimates are accurate, annual screening programs may introduce more harm (through treatment-related morbidity) than benefit in terms of reducing cancer-specific mortality. However, most data support the contention that current screening efforts using PSA testing do not detect substantial numbers of indolent prostate cancers. In most screening studies, the cancer detection rate ranges from 7% to 10%, which is substantially lower than the 50% to 70% incidence of indolent cancer in autopsy studies.[7,8] In a recent study, less than 10% of screening-detected cancers were classified as clinically insignificant.[7]

Recommendations

Formal guidelines on screening. Guidelines from professional societies and governmental organizations reflect the current uncertainty about the benefits of widespread prostate cancer screening. The American Cancer Society (ACS) and the American Urological Association (AUA) recommend annual screening with the PSA test and DRE beginning at age 50 years for men who have a life expectancy of 10 or more years.[14,15] Screening should begin earlier—at age 40 years—in men at high risk for developing prostate cancer on the basis of sub-Saharan African ancestry and/or the presence of an affected first-degree relative, particularly if the diagnosis in the relative was made before age 55.[14,15] However, mass prostate cancer screening is not endorsed by the United States Preventive Services Task Force (USPSTF), owing to the lack of definitive evidence that the benefits of screening outweigh the risks.[16] The USPSTF recommends that physicians discuss with patients the potential but uncertain benefits of screening and the possible risks before ordering a PSA test.

Authors' recommendations on screening. Despite a lack of conclusive evidence regarding the benefits of prostate cancer screening and the conflicting recommendations, PSA testing is widely practiced in North America and in many parts of Europe. An estimated 57% of American men aged 50 years or older have undergone testing with serum PSA, and the vast majority of prostate cancers are now diagnosed as a result of opportunistic PSA screening.[17,18]

The controversy surrounding prostate cancer screening is unlikely to subside until results of the PLCO and ERSPC screening trials are available. Pending those results, we believe that prostate cancer screening using serum PSA level determinations and DRE should be offered to men 50 years of age or older who have a life expectancy of 10 years or more. Screening should be offered in conjunction with a discussion of its potential benefits and risks. Screening should always include serum PSA testing *and* DRE, as 25% or more of cancers will be detected in men with PSA levels less than 4.0 ng/mL. Men with risk factors for developing prostate cancer (sub-Saharan African ancestry, affected first-degree relative) should undergo PSA-based screening beginning at age 40 years **(Table 3)**. The optimal screening interval has not been defined, but the ACS and the AUA recommend annual screening.[14,15]

Recommendations for follow-up and referral. An elevated serum PSA level or prostate abnormalities on DRE are indications for prostate biopsy. A total PSA level greater than 4.0 ng/mL has traditionally been the threshold for recommending prostate biopsy, although a lower threshold (2.0 ng/mL) may be considered in men younger than 60 years.[19] The probability of finding prostate cancer on biopsy when these indications are present is 20% to 30%.[19]

The PSA level may be elevated by conditions other than prostate cancer, such as benign prostate disease (benign prostatic hyperplasia and acute or chronic prostatitis), urinary retention, urethral instrumentation, DRE, and sexual activity. Before considering prostate biopsy for an isolated PSA elevation, the PSA level should be confirmed by a repeat measurement several weeks later, as 44% and 40% of men with an isolated PSA elevation greater than 4.0 ng/mL and 2.5 ng/mL, respectively, will have a normal PSA reading at one or more subsequent visits.[20]

Referral for prostate biopsy should also be made when there are abnormalities on DRE such as a palpable nodule, induration, or asymmetry. Normally the prostate should be symmetrical and should have the consistency of the thenar eminence.

In an analysis of patients enrolled in the Prostate Cancer Prevention Trial, the main predictors of

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TABLE 3
Screening recommendations for urologic cancers

Cancer	Screening options and their major limitations	Recommendations for general population	Target populations
Prostate	Prostate-specific antigen (PSA) test –Suboptimal specificity –May detect "insignificant" cancers Digital rectal examination (DRE) –Low sensitivity	No definitive evidence for reduction in prostate cancer mortality, but ample evidence supporting screening with PSA test and DRE for early diagnosis of prostate cancer Annual screening starting at age 50 (age 40 in target populations), provided that patient has life expectancy >10 years, is recommended by several professional societies and should be offered to and discussed with each patient	Men of sub-Saharan African ancestry Men with an affected first-degree relative
Bladder	Dipstick of urine –Hematuria is often intermittent –Incidence too low –Suboptimal specificity Cytology –Low sensitivity –Too expensive Tumor markers –Low sensitivity –Too expensive	Data do not justify generalized screening Focus should be on target populations; primarily use dipstick of urine to screen for hematuria in this setting Urologic referral indicated if microscopic or gross hematuria detected	Current or former tobacco users, especially older men Persons with occupational exposure in chemical, textile, or rubber industries Persons with past exposure to phenacetin, cyclophosphamide, or pelvic radiation therapy Patients with chronic UTIs or neurogenic bladder Patients with spinal cord injury with intermittent catheterization or indwelling catheter
Kidney (RCC)	Dipstick of urine –Incidence too low –May detect benign/indolent tumor –Hematuria often not present Ultrasonography –Too expensive –Yield too low to justify –Suboptimal specificity	Data do not justify generalized screening Focus should be on target populations; primarily use ultrasonography or computed tomography to screen for renal mass in this setting Urologic referral indicated if mass is found	Persons with history suggestive of familial RCC, such as von Hippel-Lindau disease Patients with end-stage renal failure (screen selectively)
Testicular	Physical exam and self-exam –Examiner-dependent	Data do not justify generalized screening Focus should be on target populations; primarily use clinical examination and selective ultrasonography for symptoms or signs in this setting	Patients with the following: –History of undescended testis –Atrophic testis –Male infertility –Personal or family history of testicular cancer –Microlithiasis on testicular ultrasonography

RCC = renal cell carcinoma; UTI = urinary tract infection

prostate cancer on biopsy were the total serum PSA level, a positive family history, an abnormal DRE, and the absence of a prior negative prostate biopsy.[19]

BLADDER CANCER

Epidemiology and natural history

Bladder cancer is the fourth most common cancer in men and the eighth most common in women, and it represents a major source of morbidity and mortality in the United States **(Table 1)**.[1,21] Overall, this cancer is three to four times more common in men than women, and most cases are seen in the sixth through ninth decades of life.[22,23]

Bladder cancer is a prototype of the environmentally related cancer. Carcinogens filtered by the kidney bathe the lining of the bladder, leading to a field effect—ie, the entire urothelium is at risk. The preclinical phase is relatively short; bladder cancer is

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rarely discovered at autopsy.[22] Multifocal disease is frequently found at presentation, and recurrence is common during longitudinal follow-up.[23]

Two clinical pathways predominate for bladder cancer. The first, which represents 50% to 60% of cases, is characterized by low-grade, noninvasive tumors that tend to recur but rarely progress.[23] The second pathway, on the other hand, is characterized by high-grade disease that not only can recur but also can progress to invasive disease.[23]

Symptoms, presentation, and screening options

Bladder cancer commonly presents with painless hematuria, although about 10% to 20% of patients present primarily with irritative voiding symptoms.[23] Gross hematuria is a major warning sign of cancer and always mandates urologic evaluation, but microscopic hematuria is also commonly associated with bladder cancer.[22]

It is critical that distracting diagnoses not dissuade the clinician from pursuing an etiologic explanation for hematuria. For instance, a substantial minority of patients receiving warfarin who present with hematuria are subsequently determined to harbor urologic cancer—in other words, warfarin was *not* the culprit. Hence, just as we would not accept hemorrhoids as the cause of rectal bleeding in a middle-aged man until cancer had been ruled out, we must pursue clear delineation of the origin of hematuria in patients on anticoagulant therapy.

Dipstick urinalysis is the primary screening method for bladder cancer, although cytology has also been proposed, as has testing for molecular markers that detect tumor antigens and other abnormalities.

Rationale for screening

The rationale for screening is to detect high-grade bladder tumors before they become invasive, when the likelihood of achieving a cure is still high. Once high-grade tumors become invasive, radical treatments are needed that often entail substantial morbidity. Even if treated in such an aggressive manner, about 50% of patients with high-grade invasive bladder cancer will die of disease progression.[22,24]

However, screening is not likely to have a substantial impact in patients with low-grade bladder tumors, who represent 50% to 60% of bladder cancer cases, as low-grade tumors are not life-threatening and the benefit of their early diagnosis is highly debatable.[23]

Arguments against screening

The prospect of screening for bladder cancer poses inherent problems since the overall incidence of this cancer is low (about 20 per 100,000 population per year[1]) and only a minority of patients—those with high-grade disease that has not yet become invasive—might benefit from screening. For these reasons, a screening test would need to be very inexpensive and highly specific to be considered cost-effective. In addition, hematuria, the main warning sign of bladder cancer, tends to be intermittent, so repetitive screening is required.[22,24]

The current literature supports these assertions. Most studies have focused on older men and have used urine dipstick analysis to screen for hematuria. In one large study using a single test to look for hematuria, no substantial change in the incidence of urologic cancers was found between screened and unscreened men.[22]

Studies using repetitive dipstick testing for hematuria have been more promising but remain inconclusive. In one such study of 2,356 asymptomatic men 60 years of age or older, bladder cancer was found in 17 subjects, and no tumors were muscle-invasive.[25] However, after 7 years of follow-up, 3 of the 9 subjects with high-grade tumors died of cancer progression, suggesting that the natural history of the disease cannot always be altered even if detected through screening.[25] In a landmark study, Messing et al screened 1,575 asymptomatic men 50 years of age or older with a urine dipstick and compared their outcomes with those of a control group of nonscreened subjects from a local cancer registry.[24] A total of 21 bladder cancers were screen-detected, and the incidence of invasive cancer was substantially lower in the screened population than in the control group (4.8% vs 23.9%, respectively).[24] Cancer-related mortality was also lower in the screened population (0% vs 16.4%).[22,24] Selection bias and biases in lead time or length time may have contributed to these results, however, and a randomized trial would be required to provide definitive data on the value of screening in this manner.

Recommendations

Most authorities believe that screening the general population for bladder cancer is not likely to be cost-effective, and routine urinalysis has not been advocated as a part of routine preventive care by most major medical organizations. Rather, urinalysis is recommended for select patients with lower urinary tract symptoms, hypertension, diabetes, or other specific indicators of urologic or renal pathology (hematuria, flank pain, unexplained peripheral edema).[26,27]

Thus, a more rational approach is to focus on target populations that have an increased incidence of bladder cancer **(Table 3)**, keeping in mind

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the following risk factors:

Tobacco use, which is the single most common and most important predisposing factor, increasing the risk of bladder cancer twofold to fourfold.[23]

Occupational exposure, most notably in the chemical, textile, and rubber industries. Workers in these industries are at a 20-fold or greater increased risk of developing bladder cancer relative to the general population. The latency period is 15 to 20 years, on average.[23]

Exposure to phenacetin or cyclophosphamide, or a history of pelvic radiation therapy.[23]

Chronic urinary tract infection or neurogenic bladder (chronic inflammation is thought to be the etiology).[22,23]

Spinal cord injury requiring intermittent catheterization or indwelling catheter. Screening in this setting has been shown to be nonproductive, but all patients with gross hematuria should be evaluated.[22,23]

With the exception of the last subgroup, routine screening should include an occasional urinalysis; if this demonstrates 3 or more red blood cells per high-power field (40×), formal urologic evaluation should be pursued, including urine cytology, upper urinary tract imaging, and cystoscopy.[27] Formal biopsy should be obtained if cytology or cystoscopy reveal potentially suspicious findings.

Cytology has also been proposed as an intermediate screening tool to stratify patients with microhematuria into those who need further intensive evaluation and those who require only continued surveillance.[22,27] This approach has been advocated in patients with occupational exposure in an effort to reduce the number of invasive procedures, but its ultimate utility has not been determined. Urine cytology provides excellent specificity but suboptimal sensitivity: although it will reduce the number of required cystoscopies, it also will lead to a missed diagnosis in many patients.[22,27]

Molecular markers that can detect tumor antigens, nuclear matrix proteins, chromosomal changes, and other abnormalities associated with bladder cancer have also been studied and in general provide better sensitivity than does urine cytology.[28] Like cytology, however, most of these tests are too expensive to play a prominent role in generalized screening programs.

Actually, the patient group at highest risk for developing bladder cancer consists of those with a history of the disease.[29] More than 50% of cases will recur with time, and intensive surveillance with periodic urine cytology and cystoscopy has traditionally been recommended.[29] These patients should be followed by a urologist, although a subgroup of low-risk patients may be released back into the care of their primary care physician after 5 years if they remain continuously cancer-free. The latter group should undergo a yearly urinalysis.[28]

KIDNEY CANCER

Epidemiology

Kidney cancer, or renal cell carcinoma (RCC), has a relatively low incidence in the United States: 8.9 cases per 100,000 population per year.[30]

Symptoms, presentation, and screening options

The classic symptoms of RCC, including gross hematuria, palpable mass, or flank pain, are now uncommon; today most patients present incidentally. This is decidedly fortunate, as all signs and symptoms related to RCC have negative prognostic implications.[31]

The screening modalities that have been studied for detection of RCC include dipstick urinalysis, ultrasonography, and computed tomography (CT).

Rationale for screening

Several factors make screening for RCC appealing. Most important, RCC remains primarily a surgical disease requiring early diagnosis to optimize the opportunity for cure. Unfortunately, current systemic therapies for RCC have only modest efficacy, and our ability to salvage patients with more advanced disease remains limited, as reflected in the formidable mortality statistics in **Table 1**. As one might expect, several studies have demonstrated an apparent survival advantage to early or incidental diagnosis of RCC.[31] Early diagnosis can also facilitate nephron-sparing approaches and the use of less invasive modalities, such as thermal ablation.[31]

Arguments against screening

The primary factor that limits widespread screening for RCC is its relatively low incidence in the general population, as noted above.[30] Any potential screening test would need to be almost 100% specific or it would lead to a multitude of unnecessary, expensive, and potentially harmful diagnostic or therapeutic procedures. In addition, even if the test were 100% sensitive and specific, the yield from screening the general population would be so low as to not be considered cost-effective. Even when one considers populations with established risk factors for RCC, such as male sex, advanced age, and heavy tobacco use, screening would be difficult to justify because the increase in relative risk associated with each of these factors is, at most, twofold to threefold.[31]

Another factor that argues against generalized screening for RCC is the prevalence of clinically

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insignificant tumors such as renal adenomas, which have an autopsy incidence of 10% to 20%, and other benign or indolent tumors.[31]

The current literature on the use of dipstick urinalysis, ultrasonography, or CT for screening for RCC substantiates these concerns. Urinalysis for hematuria is simple and inexpensive, but its yield of RCC detection in clinical studies has been exceedingly low. Many small RCC tumors are not associated with hematuria, whether gross or microscopic, since this is a parenchymal-based, rather than urothelial-based, cancer.[31] The incidence of RCC in screening studies using ultrasonography or CT has ranged from 20 to 300 per 100,000 population, somewhat higher than expected given the clinical incidence of this cancer.[32,33] These rates are still relatively low, however, and such approaches are not likely to be considered cost-effective. Overall, the yield of RCC diagnoses in such studies is still more than an order of magnitude lower than the yield of prostate cancer diagnoses from PSA-based screening, and many of the same controversies about lead and length time biases in screening for other cancers also apply to RCC.[31] Some have argued that imaging-based screening could be broadened to look for other malignancies, abdominal aneurysms, and coronary artery disease in addition to RCC, which might increase the utility and cost-effectiveness of this approach. However, solid data in support of this argument are not currently available, and this remains a controversial topic.

Recommendations

In light of the above, generalized screening for RCC is not indicated. The primary focus of screening for this cancer must be on well-defined target populations such as patients with familial RCC and those with end-stage renal failure (ESRF) or acquired renal cystic disease.[31,34,35]

About 2% to 4% of RCC cases are familial, and these comprise a number of well-characterized entities such as von Hippel-Lindau disease.[34] This disorder, which is transmitted in an autosomal dominant manner, can lead to hemangioblastomas of the central nervous syndrome, retinal angiomas, renal cysts, pheochromocytoma, and RCC. RCC in von Hippel-Lindau disease tends to be early-onset and multifocal, and patients with other manifestations of this syndrome or with a family history suggestive of von Hippel-Lindau disease or other familial forms of RCC should undergo abdominal imaging to screen for RCC.[34]

Eighty percent of patients with ESRF eventually develop acquired renal cystic disease, and 1% to 2% of patients in this subgroup develop RCC.[31,35] Overall, the relative risk of RCC appears to be about 5-fold to 20-fold higher in patients with ESRF than in the general population.[31,35] However, many patients with ESRF have a short life expectancy and RCC is typically not seen in the first few years after initiation of dialysis. A reasonable approach is to focus screening efforts on ESRF patients who do not have other major comorbidities, to delay screening until the third year on dialysis, and to start with ultrasonography and withhold CT until suspicious lesions are identified.[31]

TESTICULAR CANCER

Epidemiology

Germ cell tumors of the testis (nonseminoma and seminoma) are the most common malignancy in males aged 15 to 35 years; the lifetime risk of testicular cancer is 1 in 500.[1] The typical age at diagnosis ranges from 15 to 50 years.

Symptoms, presentation, and screening options

Symptoms related to the testicle are present in the vast majority of patients and typically include a history of a palpable testicular mass. Nevertheless, diagnostic delay is a well-recognized phenomenon of testicular cancer, and one to which both patients and physicians contribute. Patients may delay medical evaluation of a testicular mass out of embarrassment, fear, guilt, or ignorance. Additionally, physicians often may contribute to diagnostic delay through misdiagnosis or unnecessary diagnostic tests or interventions; up to one third of testicular tumors are initially misdiagnosed as epididymitis or hydrocele.[36] A relationship has been observed between the length of diagnostic delay and response to chemotherapy, with patients who are subject to delay presenting with more advanced disease that requires more intensive treatment regimens.[37]

The primary means of screening for testicular cancer is physical examination of the testicles, both by the patient himself and by his primary care provider as part of the periodic health examination. Careful testicular examination can usually differentiate pain or a mass arising from the epididymis from pain or a mass in the testicle. The presence of a hydrocele may prevent accurate assessment of the testicle, and ultrasonography of the scrotum is indicated if a patient has symptoms related to the testicle with an associated hydrocele.

Recommendations

Thanks to the development of effective chemotherapy and the integration of chemotherapy and surgery, the overall cure rate associated with testicular cancer is 96%.[38] Given the relative rarity of this disease

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(**Table 1**), its high cure rates, and the ease of detection by testicular self-examination, routine screening specifically for this disease (other than by self-examination) is not recommended and is unlikely to significantly affect the prognosis. However, patient education about regular testicular self-examination is recommended, as is the inclusion of routine testicular examination in periodic health examinations of postpubertal males until age 50.

Several risk factors for the development of testicular cancer have been identified,[39] as outlined in **Table 3**, and should prompt increased clinician vigilance in conducting testicular examinations:

A history of cryptorchidism (undescended testis) confers an 8-fold to 16-fold increased risk of developing testicular cancer.[39] Although it is controversial whether orchiopexy in early childhood reduces this risk, orchiopexy is still recommended to allow further development of the testis and to facilitate early diagnosis should a tumor occur. Periodic testicular examination should begin at puberty in these patients.

Family or personal history. Having an affected first- or second-degree relative also appears to increase risk, and patients with a personal history of testicular cancer have a 3% to 5% lifetime risk of developing a germ cell tumor in the contralateral testicle.[39]

Microlithiasis, atrophic testis, infertility. The presence of testicular microlithiasis identified on routine scrotal ultrasonography has been reported in 0.6% to 0.9% of the general male population and may be associated with a slightly increased risk of testicular cancer.[40] An increased incidence of testicular cancer has also been correlated with atrophic testis and male infertility, so patients with these conditions also merit careful scrutiny.

The potential association of the above conditions with development of testicular cancer should be conveyed to the postpubertal male patient younger than age 50, and the importance of testicular self-examination and routine clinical assessment should be emphasized. Equivocal or suspicious findings from a physical examination should prompt ultrasonographic examination of the testes, and urologic referral should be pursued if any intratesticular abnormalities are found.

REFERENCES

1. **Jemal A, Siegel R, Ward E, et al.** Cancer statistics, 2006. CA Cancer J Clin 2006; 56:106–130.
2. **Wilson SS, Crawford ED.** Screening for prostate cancer: current recommendations. Urol Clin North Am 2004; 31:219–226.
3. **Etzioni R, Legler JM, Feuer EJ, Merrill RM, Cronin KA, Hankey BF.** Cancer surveillance series: interpreting trends in prostate cancer—part III: quantifying the link between population prostate-specific antigen testing and recent declines in prostate cancer mortality. J Natl Cancer Inst 1999; 91:1033–1039.
4. **Bartsch G, Horninger W, Klocker H, et al.** Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. Urology 2001; 58:417–424.
5. **Roberts RO, Bergstralh EJ, Katusic SK, Lieber MM, Jacobsen SJ.** Decline in prostate cancer mortality from 1980 to 1997, and an update on incidence trends in Olmsted County, Minnesota. J Urol 1999; 161:529–533.
6. **Labrie F, Candas B, Dupont A, et al.** Screening decreases prostate cancer death: first analysis of the 1988 Quebec prospective randomized controlled trial. Prostate 1999; 38:83–91.
7. **Loeb S, Gonzalez CM, Roehl KA, et al.** Pathological characteristics of prostate cancer detected through prostate specific antigen based screening. J Urol 2006; 175:902–906.
8. **van der Cruijsen-Koeter IW, Vis AN, Roobol MJ, et al.** Comparison of screen detected and clinically diagnosed prostate cancer in the European Randomized Study of Screening for Prostate Cancer, Section Rotterdam. J Urol 2005; 174:121–125.
9. **Bianco FJ Jr, Scardino PT, Eastham JA.** Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology 2005; 66(Suppl 5):83–94.
10. **Schroder FH.** Screening for prostate cancer. Urol Clin North Am 2003; 30:239–251, viii.
11. **Bill-Axelson A, Holmberg L, Ruutu M, et al.** Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005; 352:1977–1984.
12. **Albertsen PC, Hanley JA, Fine J.** 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005; 293:2095–2101.
13. **Draisma G, Boer R, Otto SJ, et al.** Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003; 95:868–878.
14. **Smith RA, Cokkinides V, Eyre HJ.** American Cancer Society guidelines for the early detection of cancer, 2006. CA Cancer J Clin 2006; 56:11–25.
15. Prostate-specific antigen (PSA) best practice policy. American Urological Association (AUA). Oncology (Williston Park) 2000; 14:267–280.
16. **U.S. Preventive Services Task Force.** Screening for prostate cancer: recommendation and rationale. Ann Intern Med 2002; 137:915–916.
17. **Cooperberg MR, Moul JW, Carroll PR.** The changing face of prostate cancer. J Clin Oncol 2005; 23:8146–8151.
18. **Ross LE, Coates RJ, Breen N, Uhler RJ, Potosky AL, Blackman D.** Prostate-specific antigen test use reported in the 2000 National Health Interview Survey. Prev Med 2004; 38:732–744.
19. **Thompson IM, Pauler-Ankerst D, Chi C, et al.** Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst 2006; 98:529–534.
20. **Eastham JA, Riedel E, Scardino PT, et al.** Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. JAMA 2003; 289:2695–2700.
21. **Botteman MF, Pashos CL, Redaelli A, Laskin B, Hauser R.** The health economics of bladder cancer: a comprehensive review of the published literature. Pharmacoeconomics 2003; 21:1315–1330.
22. **Kryger JV, Messing E.** Bladder cancer screening. Semin Oncol 1996; 23:585–597.
23. **Kirkali Z, Chan T, Manoharan M, et al.** Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 2005; 66(Suppl 6A):4–34.
24. **Messing EM, Bram LL, Young TB, et al.** Comparison of bladder cancer outcome in men undergoing hematuria home screening versus those with standard clinical presentations. Urology 1995; 45:387–397.
25. **Mayfield MP, Whelan P.** Bladder tumors detected on screening: results at 7 years. Br J Urol 1998; 82:825–828.
26. **Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR.**

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Screening for proteinuria in US adults. A cost-effectiveness analysis. JAMA 2003; 290:3101–3114.
27. **Grossfeld GD, Carroll PR.** Evaluation of asymptomatic microscopic hematuria. Urol Clin North Am 1998; 25:661–676.
28. **Lokeshwar VB, Habuchi T, Grossman HB, et al.** Bladder tumor markers beyond cytology: international consensus panel on bladder tumor markers. Urology 2005; 66(Suppl 6A):35–63.
29. **Donat SM.** Evaluation and follow-up strategies for superficial bladder cancer. Urol Clin North Am 2003; 30:765–776.
30. **Landis SH, Murray T, Bolden S, Wingo PA.** Cancer statistics, 1999. CA Cancer J Clin 1999; 49:8–31.
31. **Cohen EB, Campbell SC.** Screening for renal cell carcinoma. In: Novick AC, Bukowski RM, eds. Renal Cell Carcinoma: Molecular Biology, Immunology, and Clinical Management. Totowa, NJ: Humana Press; 2000:93–110.
32. **Tosaka A, Ohya K, Yamada K, et al.** Incidence and properties of renal masses and asymptomatic renal cell carcinoma detected by abdominal ultrasonography. J Urol 1990; 144:1097–1099.
33. **Tsuboi N, Horiuchi K, Kimura G, et al.** Renal masses detected by general health checkup. Int J Urol 2000; 7:404–408.
34. **Lineham WM, Walther MM, Zbar B.** The genetic basis of cancer of the kidney. J Urol 2003; 170:2163–2172.
35. **Ishikawa I, Saito Y, Onouchi Z, et al.** A ten-year prospective study on the development of renal cell carcinoma in dialysis patients. Am J Kidney Dis 1990; 16:452–458.
36. **Bosl GJ, Vogelzang NJ, Goldman A, et al.** Impact of delay in diagnosis on clinical stage of testicular cancer. Lancet 1981; 2:970–973.
37. **Stephenson AJ, Russo P, Kaplinsky R, Sheinfeld J.** Impact of unnecessary exploratory laparotomy on the treatment of patients with metastatic germ cell tumor. J Urol 2004; 171:1474–1477.
38. **International Germ Cell Cancer Collaborative Group.** International Germ Cell Consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997; 15:594–603.
39. **Kramer JL, Greene MH.** Hereditary testicular cancer. In: Vogelzang NJ, Scardino PT, Shipley WU, Debruyne FMJ, Linehan WM, eds. Comprehensive Textbook of Genitourinary Oncology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:558–562.
40. **Serter S, Gumus B, Unlu M, et al.** Prevalence of testicular microlithiasis in an asymptomatic population. Scand J Urol Nephrol 2006; 40:212–214.

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