Prostate cancer is the most commonly diagnosed nonskin cancer in men, with 233,000 new cases estimated for 2014. Nearly 30,000 deaths are predicted for 2014, second only to lung and bronchial cancer deaths. Early diagnosis is key to improving patient survival rates. Screening efforts have dramatically increased the detection rate, and now, 90% of new diagnoses are caught at the early stage of disease. However, new data are driving controversial changes to screening and treatment recommendations.

**Learning objectives**

- Describe current prostate screening guidelines.
- Identify patient history, physical examination, and diagnostic test findings that support the diagnosis of prostate cancer.
- Develop treatment strategies for various clinical stages of prostate cancer.

New recommendations in prostate cancer screening and treatment

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**ABSTRACT**

Prostate cancer is the most commonly diagnosed nonskin cancer in men, with 233,000 new cases estimated for 2014. Nearly 30,000 deaths are predicted for 2014, second only to lung and bronchial cancer deaths. When prostate cancer is diagnosed early and still locally confined, the 5-year survival is about 100%. However, if the disease is advanced and the cancer has spread to distant sites, the 5-year survival drops to 33%. Known risk factors for the disease include advanced age, family history, and black race. Screening efforts have dramatically increased the detection rate, and most new diagnoses are made at the early stage of disease.

**Keywords:** prostate cancer, prostate-specific antigen, Gleason score, vaccine, screening, androgen deprivation therapy

**Changes in screening recommendations**

Men diagnosed with prostate cancer are usually asymptomatic and diagnosed by screening efforts using digital rectal examination (DRE) and serum prostate-specific antigen (PSA) assay. Men who are asymptomatic at diagnosis are more likely to have advanced disease. Mortality from prostate cancer has significantly declined over the past several decades, thought to be due at least in part to improved screening and detection with the development of the PSA assay.

Although diagnosing the disease at an early stage is advantageous, routine screening of asymptomatic men has no significant benefit, according to the US Preventive Services Task Force’s (USPSTF’s) comprehensive review of meta-analyses of the US Prostate, Lung, Colorectal, and
New recommendations in prostate cancer screening and treatment

**Key points**

- Prostate cancer is the most commonly diagnosed nonskin cancer in men, with a 1 in 6 lifetime risk.
- Routine PSA screening of asymptomatic men is no longer recommended by the USPSTF. Choosing to screen should be a mutual decision between the primary care provider and the patient, with new data to suggest that longer screening intervals may be appropriate.
- Symptoms that raise suspicion include hesitancy, dribbling, incomplete voiding, poor stream, overflow incontinence, and bone pain.
- The patient's goals, life expectancy, and disease stage all contribute to selecting the treatment.

Ovarian (PLCO) Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSSPC). In fact, screening only prevents about 1 death per 1,000 men. The risks associated with screening include false positive PSA result (120 per 1,000), pathologic prostate cancer diagnosis (110 per 1,000), serious cardiovascular events associated with long-term androgen deprivation therapy (2 per 1,000), erectile dysfunction secondary to treatment (29 per 1,000), and urinary incontinence secondary to treatment (2 per 1,000). Consequently, the USPSTF has issued a position statement against routine PSA screening of asymptomatic men. This position has been reinforced by the American Academy of Family Physicians (AAFP). The American Urological Association (AUA) initially was opposed to this new screening paradigm but recently issued new clinical guidance based on independent review of the data. Table 1 compares current screening recommendations from the USPSTF and AUA. The most notable difference is that the AUA recommends shared decision making for patients between ages 55 and 69 years at average risk as well as patients younger than 55 years with known risk factors.

This puts the onus on the primary care provider (PCP) to switch gears from automatically ordering a PSA for all men 50 years and older to engaging patients in a discussion of risks versus benefits of prostate cancer screening. The USPSTF acknowledges that many providers will still choose to use PSA screening and encourages them to talk with patients so an informed decision can be made. This topic is most appropriately discussed with men ages 55 to 69 years, who have more than 10 years life expectancy, and/or who have a family history of prostate cancer or other predisposing factor.

In situations where the PCP and patient have decided to proceed with screening, recent research supports a prolonged screening interval in certain situations. For example, a recent study by Vickers and colleagues proposes three PSA values obtained around ages 45, 50, and 60 years may be sufficient to determine prostate cancer risk for most men. Weight and colleagues have published a prospective screening study finding that men ages 40 to 49 years with a baseline PSA less than 1 ng/mL have a 0.6% risk of prostate cancer diagnosis by age 55 years; men with a baseline PSA greater than 1 ng/mL have a 15.6% risk of prostate cancer diagnosis by age 55 years. This suggests that the screening interval may be individualized based on risk stratification. These studies support screening more intelligently as opposed to routine annual screening of all patients. The screening recommendations from any organization do not change the role of PSA monitoring in patients who have been diagnosed with prostate cancer.

PCPs will still need to recognize clinical signs and symptoms of prostate cancer, identify patient characteristics associated with a higher risk of aggressive disease, and determine when screening is appropriate.

**DIAGNOSING PROSTATE CANCER**

Prostate cancer is considered a disease of older men, rarely diagnosed before the late 40s. Deaths from prostate cancer rarely occur before the age of 60 years. Many studies have attempted to identify lifestyle choices which may alter a man’s risk for prostate cancer, but surprisingly, no link has been proven between prostate cancer and smoking, sexual history, or past medical history, including prostatitis or benign prostatic hyperplasia (BPH). Although prostate cancer can affect men of any racial or ethnic background, black men have an almost doubled incidence and greater than doubled mortality compared with white and Hispanic men. Black men are more likely to be diagnosed at an earlier age, later stage, and with a more aggressive tumor than white men. Patient characteristics found to be associated with low-risk tumors include white race, younger age, and living in the southern United States. PCPs should take these facts into consideration when initiating a discussion with patients on prostate cancer screening.

Although most prostate cancer cases are diagnosed by screening, other clinical signs and symptoms warrant further investigation. Lower urinary tract symptoms such as hesitancy, dribbling, incomplete voiding, poor stream,
and overflow incontinence may indicate dysfunction secondary to a mass effect. This mass effect could be prostate cancer that is large or locally invasive, but more frequently is BPH, which is very common in aging men. Rarely, prostate cancer can metastasize to the spinal cord and cause neurogenic voiding symptoms such as urinary retention. The lymph nodes are a more common site of metastasis, and should be suspected in patients who present with lymphedema of the distal extremities. The most common site of metastasis is the axial skeleton; when the cancer has progressed to this stage, men may present with chronic back or other bone pain as well as pathologic fractures. Table 2 lists diagnoses that should be considered alongside prostate cancer and symptoms associated with each. For these reasons, the clinical interview for annual checkups in men over age 50 years should include the genitourinary, neurologic, and musculoskeletal reviews of systems so that subtle symptoms of prostate cancer are not overlooked.

High-risk patients with a review of symptoms positive for one or more of the above symptoms require a focused physical examination. The most important physical examination if prostate pathology is suspected is the DRE, which evaluates prostate volume, homogeneity, and nodularity. Diffuse enlargement of the prostate with homogeneity and firmness of the gland is more consistent with BPH. A prostate with prostate cancer may or may not be enlarged, but would more likely have areas of induration or one or more nodules. If the prostate is nodular upon DRE, then the chance that lower urinary tract symptoms are due to cancer increases to 50%. Other potential symptoms of prostate cancer include gait disturbance, debility, bone pain, and pain in the lower extremities.

**TABLE 2. Differential diagnosis of prostate cancer**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>Joint pain, stiffness, gait disturbance, debility</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>Hesitancy, straining, dribbling, frequency, nocturia, urgency</td>
</tr>
<tr>
<td>Bladder disorders</td>
<td>Dysfunctional voiding, hematuria, dysuria</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Bone pain, weakness, fatigue, weight loss</td>
</tr>
<tr>
<td>Musculoskeletal injuries</td>
<td>Trauma, bruising, muscle cramps, or spasms</td>
</tr>
<tr>
<td>Primary bone tumors</td>
<td>Bone pain, persistent swelling, pathologic fractures</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>Fever; chills; dysuria; nocturia; frequency; urgency; dribbling; hesitancy; lower back, abdominal, or groin pain; flu-like symptoms</td>
</tr>
<tr>
<td>Radiculopathy</td>
<td>Dermatomal nerve pain, paresthesias, motor deficits</td>
</tr>
<tr>
<td>Spinal disorders</td>
<td>Back or bone pain, stiffness, gait disturbances</td>
</tr>
</tbody>
</table>

Other potentially important physical examinations that may be relevant in suspected metastatic disease include lymph node palpation, lower extremity neurologic testing, musculoskeletal range of motion, and inspection of the lower extremities for asymmetry.

**DIAGNOSTIC STUDIES**

**Tumor markers**

PSA is a serine protease glycoprotein that is specifically secreted by epithelial cells of the prostate. PSA testing is traditionally used in screening, evaluating therapeutic response, and monitoring for disease recurrence. PSA normally increases with certain conditions, including advanced age, BPH, prostatitis, prostatic massage, cystoscopy, and needle biopsy. Because an elevated PSA is not specific for cancer, the PSA result should be interpreted in an appropriate context using age-adjusted PSA values. One way to assist in distinguishing cancer-related PSA elevation from other causes is to measure the free to total PSA ratio, which often is decreased in patients with prostate cancer. Other PSA metrics used clinically include PSA velocity and doubling time, both of which are also monitored in patients with known disease or who have undergone radical prostatectomy.

Novel tumor markers such as PCA3 and TMPRSS2:ERG are not yet routinely used in clinical decision making for patients with prostate cancer; however, numerous issues with the use of PSA are driving research to identify novel biomarkers. PCA3 is a noncoding RNA product specifically expressed by prostate cancer. The main advantage of PCA3 as a biomarker is its independence from factors known to influence PSA levels, such as prostate size, patient age, and patient’s prostate medication status. PCA3 also is a sensitive detection biomarker for the precancerous lesion known as high-grade prostatic intraepithelial neoplasia. Gene fusions are well-known in several cancers, but the TMPRSS2:ERG gene fusion is specifically found in prostate cancer samples. TMPRSS2:ERG positivity may predict tumor aggressiveness and response to hormone therapy. Both PCA3 and TMPRSS2:ERG are detectable by urine assay.

**Transrectal ultrasound (TRUS)**

This test evaluates the prostate gland and is commonly used to facilitate biopsy. TRUS with biopsy is the first-line imaging study for patients with PSA greater than age-specific cutoff values, PSA velocity greater than 0.75 per year, or abnormal DRE. Prostate cancer lesions may appear as hypoechoic masses. The contour of the prostate gland as well as the contour of any hypoechoic lesion is examined for irregularities, which may be suggestive of extracapsular or seminal vesicle invasion. In locally confined tumors associated with minimal PSA elevations, TRUS is commonly the only imaging indicated.
MRI and CT Although the positive predictive value for MRI and TRUS for detection of local invasion of the primary prostate cancer lesion is similar, MRI and CT have the advantage of visualizing regional lymph nodes. MRI is preferred over CT for imaging the primary lesion due to poor discrimination between the prostate gland and surrounding structures. Functional applications of MRI, such as magnetic resonance spectroscopic imaging (MRSI), also enhance clinical evaluation by determining the levels of prostatic metabolites, including choline and citrate. Better resolution to further delineate extracapsular invasion is achieved using 3-Tesla MRI with endorectal coils. Either MRI or CT would be appropriate to rule out distant metastasis. Any suspicious lymph nodes discovered on physical examination or on MRI should be biopsied using core needle biopsy.

Bone imaging Because the bones are the most frequent site of prostate cancer metastasis, radionuclide bone scan would appear to be indicated for the staging of all patients. But fewer than 10% of patients actually present with bony metastases, so screening bone scans in all newly diagnosed patients is controversial. The most recent research suggests indications for a bone scan should include PSA greater than 20 ng/dL, a poorly differentiated tumor with evidence of local invasion, histopathologic Gleason score of 7 or greater, palpable disease, and symptoms of metastatic spread. In patients who have already undergone a radical prostatectomy, there is no benefit in performing a bone scan based solely on a biochemical recurrence without clinical evidence such as bone pain. The age group most commonly affected by prostate cancer is also commonly affected by other bone disorders such as degenerative joint disease, which could result in an abnormal bone scan. Plain bone radiographs are commonly used in combination with bone scan to rule out other simultaneous pathologies. Positron-emission tomography (PET) scans also are useful in identifying bony metastases, but do involve a higher degree of radiation exposure.

TREATMENT Treatment of prostate cancer depends on the patient’s Gleason score and clinical stage. Multiple cores taken during TRUS-guided needle biopsy are examined by a pathologist for Gleason scoring, which is based on cellular architecture. Figure 1 illustrates the pathology associated with each Gleason score, which is inversely proportional to the level of differentiation. Higher Gleason scores are associated with poor prognosis, and affect clinical decision making about further evaluation and treatment.

The pathologic staging of tumors is based on the traditional tumor, node, metastasis (TNM) classification system; clinical staging is based on laboratory, imaging, and physical examination findings. Treatment options vary based on the clinical staging, and each option has potential risks, summarized in Table 3.

TREATING LOCALIZED DISEASE Active surveillance A combination of DRE, PSA testing, and repeat prostate biopsies are used to monitor disease progression. Changes consistent with cancer progression signal the need for a new discussion of therapeutic options. This approach is appropriate in patients who have low-risk, localized disease with 3+3 Gleason score, and who may be at risk for complications from more-aggressive treatments.

Radical prostatectomy One of two curative therapies for localized prostate cancer, a radical prostatectomy can be performed as an open, laparoscopic, or robot-assisted surgery. Radical prostatectomy is recommended for men with intermediate or high-risk cancers with Gleason scores of 7 or greater. Even with complete resection of the prostate gland, seminal vesicles, and surrounding tissue, recurrence of locally advanced cancer occurs in 30% of patients. Adverse reactions to radical prostatectomy,
regardless of surgical technique, include erectile and urinary dysfunction.28

**Radiation therapy** An independent curative treatment for localized disease, radiation therapy can be used as an adjuvant treatment after radical prostatectomy with positive surgical margins.14,27 New technology allows for a focused beam of radiation (external beam radiation therapy [EBRT]) with minimal damage to surrounding tissues. Another commonly used method of radiation therapy is brachytherapy, in which small radioactive seeds are permanently implanted in the prostate to destroy surrounding tissue.15 Meta-analysis of clinical trials indicates that brachytherapy is associated with better outcomes in low-risk patients with prostate cancer, and EBRT is typically more successful in patients with intermediate-risk disease.28

**Cryosurgery** Less commonly used than radical prostatectomy and radiation, cryosurgery is a minimally invasive technique with fewer complications than other interventions. Adverse reactions include erectile dysfunction, hematuria, dysuria, and pain.29 Ultrasound is used to guide hollow needles into the prostate. Liquid nitrogen is circulated through the hollow needles, freezing and subsequently killing the surrounding tissue.16 This approach is often used for patients with localized disease who are unfit for traditional surgery or have limited life expectancy.27

**TREATING METASTATIC DISEASE**

**Androgen deprivation therapy** Because primary prostate cancer is initially hormone-dependent for growth, one method to “starve” the cancer is to inhibit androgen hormones. This can be accomplished surgically by orchietomy or by using drugs acting on targets such as the pituitary-hypothalamic axis, adrenal glands, testis, or on the prostate cells themselves.16 Orchietomy and luteinizing hormone-releasing hormone analogs are considered first-line androgen deprivation therapy strategies. The past few years have seen a new crop of drugs earn FDA approval for advanced prostate cancer (Table 4). Two novel anti-androgen drugs have been approved within the last 3 years for patients with metastatic castrate-resistant prostate cancer who have failed first-line androgen deprivation therapy. Abiraterone inhibits a key androgen synthesis enzyme; enzalutamide inhibits nuclear translocation and subsequent DNA binding of the androgen receptor.30 One systematic review of clinical trials showed that earlier initiation of androgen deprivation therapy was associated with better outcomes, increased time to progression, and reduced comorbidities in patients with advanced disease.31

General adverse reactions to androgen deprivation therapy include fatigue, muscle wasting, increased bone loss, and increased adiposity, all of which can lead to secondary effects, such as increased risk for bone fractures, insulin resistance, and type 2 diabetes. Another serious adverse reaction to long-term androgen deprivation therapy is increased cardiovascular risk, which should be addressed and monitored by the PCP.32

**Bone-targeting agents** Bisphosphonates are often used as an adjunct therapy to prevent skeletal-related events, including osteoporosis and associated bone pain. Bisphosphonates are incorporated into osteoclasts and prevent bone resorption.33 Up to 10% of patients on bisphosphonate therapy will experience osteonecrosis of the jaw, a serious adverse reaction.34

One alternative to bisphosphonate therapy associated with fewer adverse reactions is denosumab, a humanized monoclonal antibody against receptor activator of NFκB ligand (RANK-L). RANK-L is the major osteoclast stimulatory factor. A recent review of three clinical trials showed a significant improvement in onset of skeletal-related effects with denosumab as compared with bisphosphonates.35 A newer bone-targeting agent, radium-223, was approved in 2013 for castrate-resistant prostate cancer with symptomatic bone metastases. Shown to improve overall survival by about 4 months, this alpha-particle emitter is a calcium mimic that is preferentially incorporated at sites of high bone turnover, such as metastatic lesions.30,36

**Chemotherapy** Chemotherapy usually is reserved for patients with metastatic disease or patients whose disease has progressed despite first- and second-line androgen deprivation therapy. Docetaxel, a plant alkaloid that inhibits microtubule formation during mitosis, was the first chemotherapeutic agent used that improved overall survival; it remains a mainstay of therapy for patients with advanced disease who have progressed with androgen deprivation therapy.16 New studies are investigating docetaxel as an adjunct to other standard therapies, such as radiation or surgery, and in combination with other targeted chemotherapies.37 Cabazitaxel, a semisynthetic microtubule inhibitor, is indicated for patients with advanced disease who have progressed with docetaxel.30

**Prostate cancer vaccines** Sipuleucel-T became the first FDA-approved prostate cancer vaccine in 2010. Sipuleucel-T is an autologous cellular immunotherapy in which dendritic cells are harvested from the patient, activated by coculturing with a patented prostate cancer antigen cock-

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**Table 4. New prostate cancer therapies**

- Cabazitaxel (approved by the FDA in 2010), a semisynthetic microtubule inhibitor
- Sipuleucel-T (approved in 2010), an autologous prostate cancer vaccine
- Abiraterone (approved in 2011), an androgen synthesis inhibitor
- Enzalutamide (approved in 2012), which inhibits the nuclear translocation of the androgen receptor
- Radium-223 (approved in 2013), a calcium mimic that emits alpha particles
tail, and infused back into the same patient to stimulate an immune system attack on the cancerous cells. This therapy is only indicated for patients with early metastatic hormone-refractory prostate cancer and only provides an overall survival benefit of 4 months.

THERAPEUTIC DECISION MAKING

The process of choosing a management strategy for a patient with prostate cancer is multi-factorial and controversial. The age at diagnosis, tumor stage, and tumor grade should all be considered. As prostate cancer is generally a disease of older men, the complications of treatment options should also be made known to the patient. Patients with clinically insignificant, well-differentiated, and localized disease may decide to forgo invasive procedures that may negatively affect their quality of life. In fact, a recent study shows that there is no increased mortality 15 years postdiagnosis associated with conservative management of low-risk disease. A search of the US clinical trial database website shows more than 500 interventional clinical trials in prostate cancer, including new procedures as well as new chemical entities. As with screening, the decision of how to treat prostate cancer is best agreed upon through shared decision making between the patient and provider.

CONCLUSION

With major screening efforts occurring in the primary care setting, many cases of prostate cancer are now diagnosed very early at a localized stage. Meta-analysis of available data from the ERSPC and PLCo trials suggests that clinicians are actually overdiagnosing and aggressively treating clinically insignificant disease. Tough ethical decisions surround when to screen and how to treat patients, considering the significant risk of morbidity. The overarching theme from the AAFP and USPSTF is to discontinue routine PSA screening in asymptomatic men. The AUA continues to recommend shared decision making about screening asymptomatic men ages 55 to 69 years. The PCP should engage appropriate patients, ideally ages 55 to 69 years, in an active dialog covering their history, risk of aggressive disease, quality-of-life goals, and potential risks and benefits of screening and treatment. PCPs may also contemplate lengthening the screening interval based on individual patient risk factors and a baseline PSA value less than 1 ng/mL.

Treatment of prostate cancer is likewise becoming more conservative, taking into account patient age, comorbidities, and tumor stage and grade. PCPs should keep patients up to date on the latest research and recommendations to ensure that an informed decision is reached.

REFERENCES


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