Prostate Cancer

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1. Prevention

Advise patients who inquire about dietary and chemoprotective interventions to decrease the risk for prostate cancer that there are no proven interventions.

1.1 Advise patients that there are no proven dietary interventions to prevent prostate cancer.

Recommendations

- Advise patients that dietary changes, such as consuming less meat or other foods high in animal fat, have not been conclusively linked with a decreased risk for prostate cancer.

Evidence

- In a review, most but not all case-control studies showed a positive association between fat intake and risk for prostate cancer, and none showed a negative association. A 2002 narrative review noted that case-control studies have shown an association between fat intake and prostate cancer risk but that only 1 of 11 prospective studies reported an increase in the relative risk for prostate cancer among men with a higher intake of dietary fat (1).

Rationale

- There is conflicting evidence as to whether reducing animal-fat intake may decrease the lifetime risk for prostate cancer, and the key dietary components to avoid have not been precisely defined.

1.2 Do not recommend the use of antioxidant supplements for the prevention of prostate cancer.

Recommendations

- Advise patients that selenium and vitamin C supplements have not been shown to prevent prostate cancer and that vitamin E supplementation has been linked with higher risk for prostate cancer in healthy men.

Evidence

- A 2012 systematic review of the relationship between selenium intake and the risk for prostate cancer included 12 studies (case-control, cohort, and randomized) with 13,254 participants. Plasma selenium was associated with prostate cancer risk, with lower rates of cancer in patients with higher levels. Higher levels of toenail selenium were associated with lower rates of prostate cancer, with an RR of 0.29 (CI, 0.14 to 0.61) with toenail levels between 85 and 94 mcg/g (2).

- The Selenium and Vitamin E Cancer Prevention Trial, or SELECT Trial, was a randomized, placebo-controlled study of the effects of selenium, vitamin E, or both on prostate cancer incidence in 35,533 healthy men. SELECT was stopped early after 5 years of follow-up and found no reduction in prostate cancer risk in any of the treatment arms compared with placebo but did find a nonsignificant ($P=0.06$) increase in prostate cancer risk with vitamin E alone (3). An updated report with longer open-label follow-up of 7 years found an increase in prostate cancer in the vitamin E arm (HR, 1.17 [CI, 1.004 to 1.36]) (4).

- The Finnish randomized, controlled trial, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, compared vitamin E supplementation, beta-carotene supplementation, both, and placebo in male smokers; it was designed to study lung cancer prevention. Men receiving vitamin E had a lower incidence of prostate cancer, with relative risk reduction of 32% (CI, 12% to 47%) and a 41% (CI, 1% to 65%) reduction in prostate cancer mortality (5).

- A case-control study using prospective data from the Health Professionals Follow-up Study found no association between the use of vitamin E supplements and the risk for prostate cancer (6).
The Physicians' Health Study II was a randomized, double-blind, placebo-controlled trial of vitamin E and vitamin C for the prevention of prostate cancer. Over 14,000 male physicians participated in this four-arm study of vitamin E, 400 IU every other day; vitamin C, 500 mg/d; the combination of vitamin E and C; or placebo. Reported in 2008, with a mean follow-up of 8 years, no reduction in risk for prostate cancer was observed with the addition of vitamin E or C. The investigators concluded that their findings provided no support for the use of these antioxidants in the prevention of prostate cancer (7).

Rationale

- Antioxidants have not been shown to reduce the risk for prostate cancer.
- High levels of selenium have been associated with a lower risk for prostate cancer, but supplementation has not been shown to be beneficial.

1.3 Advise patients about the controversy of using 5-α-reductase inhibitors for prostate cancer prevention and that risks associated with their use may outweigh benefits.

Recommendations

- Do not prescribe finasteride or another 5-ARI for prostate cancer prevention in most men.
- Advise patients undergoing regular prostate cancer screening that current evidence suggests that the potential risks of using a 5-ARI, such as finasteride and dutasteride, may outweigh the potential benefits for prostate cancer prevention.

Evidence

- A 2008 guideline from ASCO and the AUA on the use of 5-ARIs for prostate cancer prevention stated that men with PSA ≤3 ng/mL who are regularly screened for prostate cancer may benefit from a discussion of the risks and benefits of 5-ARIs for prostate cancer prevention (8).
- A 2008 Cochrane review of 5-ARI for prostate cancer prevention included nine studies. Men randomized to finasteride were less likely to be diagnosed with non-screen detected prostate cancer (RR, 0.74 [CI, 0.67 to 0.83]; ARR 1.4%) and overall prostate cancer (RR, 0.74 [CI, 0.55 to 1.00]; ARR 2.9%). The review noted that one randomized trial found higher rates of more aggressive cancer in men on finasteride (9).
- Finasteride was evaluated as a chemopreventive agent in the Prostate Cancer Prevention Trial, a large 7-year trial that randomly assigned men at low risk for prostate cancer to placebo or finasteride and then monitored them with annual digital rectal examinations and serum prostate-specific antigen measurements. Men with suspicious or abnormal findings on DRE or PSA underwent biopsy. Of the 9060 men included in the final analysis, prostate cancer was detected in 18.4% of those in the finasteride arm compared with 24.4% of men in the placebo arm, giving a number-needed-to-treat of 17 ($P<0.001$), but more men in the finasteride arm had tumors of Gleason sum ≥7 (6.4% vs. 5.1% of men receiving placebo [$P<0.001$]). Men receiving finasteride reported increased rates of erectile dysfunction (67.4%) compared with placebo (61.5%) and loss of libido (65.4%) compared with placebo (59.6%) (10).
- The Reduction by Dutasteride of Prostate Cancer Events, or REDUCE, study examined the effect of dutasteride on the incidence of biopsy-detected prostate cancer in men at increased risk. The study randomly assigned more than 8000 men aged 50 to 75 years with an increased serum PSA level and a negative prostate biopsy 6 months before study entry to daily dutasteride or placebo for 4 years. Overall, men in the dutasteride group had a 22.8% lower risk for being diagnosed with biopsy-detectable prostate cancer than men in the placebo group ($P<0.0001$), but the risk reduction was mainly observed in men with low-risk tumors (Gleason sum of 5 to 6). Furthermore, during years 3 and 4, tumors with a Gleason sum of 8 to 10 were identified in 12 patients in the dutasteride group and in 1 patient in the placebo group ($P=0.003$). Finally, there was a higher
incidence of cardiac events (collectively referred to as "cardiac failure") in the dutasteride group compared with the placebo group (30 events [0.7%] vs. 16 events [0.4%]; P=0.03) (11).

Rationale

- Although 5-ARIs have been shown to reduce the total number of cases of prostate cancer and the common urinary symptoms associated with benign prostatic hypertrophy, there is concern and ongoing controversy about a possible increase in cases of high-grade prostate cancer with their use. Sexual side effects and possible cardiac effects also are a concern.

Comments

- The PCPT (10; 12) and REDUCE (11) studies treated men with 5-ARIs for 7 years and 4 years, respectively, so the effect of treatment beyond 7 years is unknown.

- The FDA analyzed data from the PCPT and REDUCE chemoprevention trials and found that the reduction of prostate cancer risk with finasteride and dutasteride was limited to tumors with a modified Gleason sum ≤6 (13). It was determined that using 5-ARIs for prostate cancer prevention meant accepting one additional high-grade tumor to prevent three to four potentially clinically relevant lower-grade tumors. Based on these findings, the Oncologic Drugs Advisory Committee of the FDA concluded that, in healthy men, the risk for more aggressive tumors outweighs the potential for chemoprevention. In December 2010, ODAC issued recommendations against prostate cancer chemoprevention labeling for finasteride and dutasteride.

- The original findings from the PCPT were reported in 2003. In 2008, the study authors published a reexamination of the original data, incorporating results of prostatectomy samples and the impact of finasteride on biopsy sensitivity for high-grade tumors. With these additional considerations, finasteride did not appear to increase the risk of high-grade prostate cancer (12).
2. Screening

Discuss screening for prostate cancer with eligible male patients.

2.1 Discuss the potential benefits, known harms, and uncertainties of prostate-specific antigen testing with standard-risk men aged 50 to 69, or beginning at age 40 to 45 in men with risk factors.

Recommendations

- Discuss prostate cancer screening with PSA testing with:
  - Men aged 50 years and older who are at average risk and have a life expectancy of 10 years or more
  - Men aged 40 to 45 who are at increased risk due to ethnicity or family history and have a life expectancy of 10 years or more
- Do not screen most men over age 69.
- Discuss annual screening in eligible patients, and pursue screening in those who request it.
- **High-value care:** Avoid screening men with a life expectancy of less than 10 to 15 years.
- Describe the potential benefits and known harms of screening, diagnosis, and treatment to patients, and individualize the decision to screen:
  - Benefits include possible lower risk for death from prostate cancer (though evidence is unclear) and treatment at an earlier disease stage
  - Potential harms include biopsy, overdiagnosis, overtreatment, and long-term side effects, including impotence, urinary irritation, and incontinence
- Consider recommending that patients abstain from ejaculating for 48 hours before the serum PSA measurement.
- Assess for use of 5-a-reductase inhibitors when interpreting PSA results, since these agents will substantially reduce the PSA level.
- Do not measure free PSA (also called PSA II) or calculate PSA density as part of routine prostate cancer screening.
- Recommend a biopsy of the prostate in patients with a serum PSA level >4.0 ng/mL or with a nodule or suspicious induration on DRE. Significant changes in PSA velocity (the rate of change in PSA levels over time) may also be considered, especially if the PSA level is between 2.5 and 4.0 ng/mL.
- See module Screening for Prostate Cancer.
- See Comparative Guidelines: Screening for Prostate Cancer.

Evidence

- A 2013 guidance statement from the American College of Physicians recommended informing average-risk men aged 50 to 69 about the potential benefits and harms of prostate cancer screening and screening only men who express a clear preference for screening. The guideline recommended against screening average-risk men under age 50 or over age 69 and men with life expectancy less than 10 to 15 years (14).
- The 2012 guideline from the U.S. Preventive Services Task Force recommended against prostate cancer screening with PSA regardless of age, racial background, or family history, citing minimal mortality benefit and known complications of screening and unnecessary treatment (15).
- A 2013 guideline from the American Urological Association on early detection of prostate cancer recommended against routinely screening men under age 40 or 70 or older, or with life expectancy less than 10 to 15 years. The guideline recommended considering screening only in high-risk men.
between the ages of 40 and 54 and shared decision-making in men aged 55 to 69. For men who are screened with PSA, the guideline recommended a 2-year screening interval and noted that high-risk men age 40 to 54 (such as black men) and some men over age 70 may benefit from screening.

- A 2010 guideline from the American Cancer Society (16) recommended that clinicians discuss the risks and potential benefits of prostate cancer screening with their male patients.

- A 2013 Cochrane review of screening for prostate cancer included five randomized trials with 341,342 participants. Overall there was no reduction in prostate cancer-specific mortality in men who were randomized to screening (RR, 1.00 [CI, 0.86 to 1.17]), but screened men were more likely to be diagnosed with prostate cancer (RR, 1.30 [CI, 1.02 to 1.65]) (17).

- Two large randomized, controlled trials have evaluated the efficacy of prostate cancer screening with serum PSA testing—the European Randomized Study of Screening for Prostate Cancer and the U.S.-based Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. These studies have reported conflicting evidence.

  - In 2009, the initial report from the European Randomized Study of Screening for Prostate Cancer was released. Over 160,000 men, age 55 to 69 years, were randomly assigned to PSA screening every 4 years vs. no structured screening program, although variations of the regimen did occur in some countries. After a median follow-up of 9 years, the cumulative incidence of prostate cancer was increased in the screening group (8.2%) compared with the control group (4.8%). The relative risk for death from prostate cancer was 0.80 (P=0.04) in the screening vs. control group. Therefore, 1410 men would need to be screened, with the identification and treatment of 48 cases of prostate cancer to prevent one death (18).

  - In 2012, an update of the ERSPC with a median follow-up of 11 years found that the death rate for prostate cancer was 0.39 in the screening group and 0.50 per 1000 person-years in the control group, with RR for prostate cancer mortality of 0.79 (CI, 0.68 to 0.91; P=0.001). For this 11-year follow-up period, 1055 men would have to be invited to be screened and 37 cancers would need to be detected to prevent one death from prostate cancer. There was no difference between the two groups in all-cause mortality (19).

  - A report from the ERSPC study site in Göteborg, Sweden (a subset of the larger ERSPC study), was published in 2010 and involved 20,000 men. The men, aged 50 to 64, were randomly assigned to serum PSA testing every 2 years or no screening. Only men with an increased PSA level were offered DRE or prostate biopsy; the PSA threshold for biopsy was 3.0 ng/dL at the start of the study and changed to 2.5 ng/dL in 2005. After a median of 14 years of follow-up, the cumulative incidence of prostate cancer was 12.7% in the screening group vs. 8.2% in the control group. The relative risk for death from prostate cancer was 0.56 (P=0.002) in the screening vs. control group. Overall, 293 (CI, 177 to 799) men needed to be screened, with the identification and treatment of 12 cases of prostate cancer to prevent 1 death due to prostate cancer (20).

  - The PLCO trial, which was reported in 2009, randomly assigned 76,693 men aged 55 to 74 to annual screening with serum PSA testing (for 6 years) plus DRE (for 4 years) or usual care. After 7 years of follow-up, there was a 22% relative increase in the diagnosis of prostate cancer with screening. There was no significant difference in prostate-specific survival (rate ratio, 1.13 [CI, 0.75 to 1.70]) between the screening and usual-care arms. Of note, the compliance with PSA testing was 85% in the screening group, whereas the rate of PSA screening in the usual-care group was 52% by the sixth year (21).

  - A 2012 update of the PLCO trial reported that after 13 years of follow-up, there was a 12% relative increase in the incidence rate of prostate cancer in the intervention arm compared with the control arm. Prostate cancer mortality did not differ between the groups, with 3.7 and 3.4 deaths per 10,000 years in the screened and control groups, respectively (RR, 1.09 [CI, 0.87 to 1.36]). There was significant trend toward decrease in the incidence of high-grade prostate cancers (Gleason score 8 to 10) in the intervention arm (RR, 0.89 [CI, 0.77 to 1.01]) (22).

  - A controlled trial of 143 men comparing serial PSA measurements in men randomly assigned to have or not to have DRE reported that DRE resulted in a mean serum PSA elevation of 0.4 ng/mL (P=0.0001). In 4 of 71 men, the PSA increased from <4.0 to >4.0 (23). Although some studies
support this finding of a small rise in PSA following DRE, other studies have reported insignificant increases on the order of 0.05 ng/mL (24; 25).

- A study of 100 men in which serum PSA was measured before ejaculation and 1 and 24 hours after ejaculation reported no change in PSA (26). Most other trials have confirmed this finding (24; 25; 27; 28). A few trials have reported that ejaculation can increase serum PSA levels for up to 48 hours (27; 29).

Rationale

- Screening may slightly reduce prostate cancer mortality but there are substantial harms, so the decision to screen is difficult and must be individualized.
- The rationale for not screening men over age 75 is based partly on the observation that 70% of men aged 80 who have no clinical history of prostate cancer are found to have latent prostate tumors at autopsy; diagnosing these tumors through screening tests and treating these men would be expected to result in more harm than benefit.
- Prostatitis, prostate biopsies, urinary tract manipulation, urinary tract infection, and prostate massage can all raise serum PSA concentration.
- There is some evidence that ejaculation and DRE can raise serum PSA levels, but in most studies the rise was rarely clinically significant.
- Appropriate thresholds for free PSA and for PSA density have not been clearly identified.

Comments

- The sensitivity of PSA (at a threshold of 4.0 mg/dL) is 21% for all cancer and 51% for high-grade cancer, with specificity of 91% (16).

2.2 Consider digital rectal examination as an adjunct to PSA in men who opt for screening and have PSA levels between 1.5 and 4 mg/dL.

Recommendations

- Consider performing DRE in patients who elect to undergo prostate cancer screening, but note that sensitivity for cancer detection is low (<50%).
- Recommend biopsy by a qualified physician in men with suspicious abnormalities (e.g., a nodule or induration) on DRE.
- See module Screening for Prostate Cancer.

Evidence

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- A 2012 update of the PLCO trial reported that after 13 years of follow-up, there was a 12% relative increase in the incidence rate of prostate cancer in the intervention arm compared with the control arm. Prostate cancer mortality did not differ between the groups, with 3.7 and 3.4 deaths per 10,000 years in the screened and control groups, respectively (RR, 1.09 [CI, 0.87 to 1.36]). There was significant trend toward decrease in the incidence of high-grade prostate cancers (Gleason score 8 to 10) in the intervention arm (RR, 0.89 [CI, 0.77 to 1.01]) (22).
- A prospective cohort study evaluated the accuracy of DRE in 10,523 men aged 54 to 76. The sensitivity was 37% with specificity of 91%, with higher sensitivity in men with higher PSA (30).
• A prospective study of 6630 men aged 49 and older having prostate cancer screening with serum PSA testing and DRE found that PSA testing was more sensitive than DRE. A total of 1167 men had a PSA level >4.0 ng/mL or a suspicious DRE and had a biopsy, and 264 tumors were detected; 216 of the 264 were associated with an elevated PSA compared with only 146 that were associated with an abnormal DRE. Forty percent of the tumors were in men with no suspicious findings on transrectal ultrasonography, or TRUS, of the prostate (31).

• A retrospective analysis evaluated data from 7195 randomly selected, previously unscreened men, who received PSA testing, DRE, and other testing as needed. The sensitivity of PSA testing was 90.5% at the first screen and 90.0% at subsequent screens (at a PSA cutoff of 4.0 ng/mL), and the sensitivity of DRE was 41.1% at the initial screen and 25.0% at subsequent screens (32).

• A prospective study evaluated the sensitivity of PSA and DRE in 6600 male volunteers aged 50 and over. The sensitivity of PSA was 82%, compared to 55% for DRE (31).

• In a prospective screening study at six different university centers involving more than 6000 men who were at least age 50, all men with a PSA level >4.0 ng/mL or an abnormal result on DRE had prostate biopsies. PPV for DRE was 21% (31).

Rationale

• DRE is inexpensive and detects some prostate cancers in men with normal serum PSA levels; a substantial number of DRE-detected tumors are clinically localized and potentially curable.

• Four large prostate cancer screening studies have documented that performing DRE increases the number of prostate cancers detected but does not reduce mortality from prostate cancer.

• Proper performance of DRE is operator dependent and requires skill and experience by the caregiver.

Comments

• The PPV of a suspicious DRE in men with a PSA level <4.0 ng/mL ranges from 10% to 20%.

• If a DRE is done, it is preferable to draw blood for the PSA measurement first, because the DRE can cause mild elevation of serum PSA.
3. Diagnosis

Evaluate new genitourinary complaints or physical findings suggesting localized or advanced prostate cancer with appropriate laboratory, imaging, and other diagnostic studies.

3.1 Ask patients about symptoms that may be associated with localized or advanced prostate cancer.

Recommendations

- Ask patients about:
  - Symptoms of bladder outlet obstruction:
    - Nocturia
    - Urinary frequency
    - Dysuria
    - Hesitancy
    - Urinary incontinence
    - Decreased force of urinary stream
  - Hematospermia or painful ejaculation
  - Pelvic pain
  - Symptoms suggesting metastatic disease (bone or back pain, weight loss, enlarged lymph nodes)
- Recognize that prostate cancer usually does not cause symptoms until it reaches an advanced stage.

Evidence

- A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer noted that most patients diagnosed with prostate cancer are asymptomatic and present to primary care.
- A study of 224 men with clinically significant prostatism (bladder outlet obstruction) reported a prostate cancer incidence of 6.7%. The positive predictive values of an elevated PSA or abnormal DRE in this population were 25% and 30%, respectively.
- A study of 54 patients presenting with acute urinary retention reported that 85% had PSA levels >4.0 ng/mL, whereas only 10% were found to have prostate cancer. The PPV of a PSA level >20.0 ng/mL was only 21%.
- A prospective study evaluated the prevalence of prostate cancer in 127 men with erectile dysfunction of at least 6 months' duration. All patients underwent PSA testing and DRE and those with abnormalities underwent biopsy. Overall, 5% of patients had prostate cancer, which was similar to the rate in the general population.
- A 1995 narrative review of hematospermia noted that prostate cancer has been identified in less than 5% of patients evaluated for hematospermia.

Rationale

- In most patients, prostate cancer is asymptomatic, but it can present with genitourinary symptoms.
- Patients with metastatic disease are more likely to be symptomatic and report bone pain, back pain, weight loss, weakness, or fatigue.

Comments
• Obstructive symptoms are more often caused by benign prostatic hyperplasia, which is more common than prostate cancer and most often affects the transitional zone in the central part of the gland that surrounds the urethra. Prostate cancer is more often found in the posterior portion of the gland away from the urethra. Nonetheless, prostate cancer can also result in obstructive symptoms.

• Acute urinary retention usually results in a substantial increase in serum PSA, regardless of whether prostate cancer is present.

3.2 Use the physical examination to document findings of localized or advanced prostate cancer in symptomatic patients.

Recommendations
• Perform a digital rectal examination to assess for signs of localized disease (e.g., prostate nodules, induration of the gland)
  • Assess for signs of metastatic disease, including:
    o Weight loss
    o Lymphadenopathy
    o Bone tenderness, especially in the spine
    o Neurologic dysfunction:
      ▪ Decreased ankle-jerk reflexes
      ▪ Increased patellar reflexes
      ▪ Lower-extremity weakness
      ▪ Perineal numbness
      ▪ Decreased rectal tone
    o Bruising or bleeding suggesting disseminated vascular coagulation

Evidence
• A 1999 narrative review discussed the typical metastatic spread of different cancers (37).
• A 2003 narrative review discussed the natural history of prostate cancer (38).

Rationale
• Prostate cancer that metastasizes most often spreads to the bones and lymph nodes.
• Spinal cord compression is a common complication of prostate cancer and can result in lower-extremity weakness, perineal numbness, urinary retention or incontinence, fecal incontinence, and pain in the back, legs, and pelvis.
• Bone metastases are often painful and may be tender.
• Men with metastatic prostate cancer often suffer from cachexia.

3.3 Obtain serum PSA levels and perform a digital rectal examination in men with obstructive urinary symptoms, impotence, hematospermia, or pelvic pain.

Recommendations
• Measure serum PSA level and perform a DRE in men who report:
  • Obstructive urinary symptoms:
    o Nocturia
    o Urinary incontinence
    o Urinary urgency
    o Frequent urination
o Urinary hesitancy or dribbling
- Impotence
- Hematospermia
- Pelvic pain

- If the patient has a urinary tract infection, allow the infection to resolve before measuring serum PSA.
- Consider recommending that men abstain from ejaculation for 48 hours before serum PSA measurement.
- Do not measure free PSA (also called PSA II) or calculate PSA density as part of a routine prostate cancer screening.
- See table Laboratory and Other Studies for Prostate Cancer.

Evidence
- A 2013 guideline from the European Society of Medical Oncology recommended checking PSA and performing DRE in patients in whom there is clinical suspicion for prostate cancer (39).
- Consensus.

Rationale
- Early prostate cancer is most often asymptomatic, but more advanced disease can result in genitourinary symptoms.

Comments
- Most patients who are diagnosed with prostate cancer have no clinical symptoms related to their cancer. Some may have symptoms of urinary outflow obstructions, although this is often due to coexisting benign prostatic hypertrophy.
- DRE may slightly increase the PSA value if performed before PSA testing, but this increase is rarely clinically significant (40).

3.4 Obtain serum PSA levels and perform a digital rectal examination in men over age 40 with signs or symptoms of metastatic prostate cancer.

Recommendations
- Measure serum PSA and perform DRE on men presenting with:
  - Significant unexplained weight loss
  - Decline in performance status
  - Bone pain
  - Lower-extremity weakness
  - Unexplained anemia or thrombocytopenia
- See table Laboratory and Other Studies for Prostate Cancer.

Evidence
- A 2013 guideline from the European Society of Medical Oncology recommended checking PSA and performing DRE in patients in whom there is clinical suspicion for prostate cancer (39).
- A 2009 systematic review of the diagnostic accuracy of PSA testing included 10 studies with 5373 participants. The quality of included studies was variable. The sensitivity of PSA ranged from 78% to 100%, with specificity varying between 6% and 66% (41).
- A 2001 narrative review on prostate cancer and spinal cord compression noted that symptomatic epidural metastases develop in 27% of patients with metastatic prostate cancer (42).
• Early prostate cancer is most often asymptomatic, but advanced disease can result in a variety of nonspecific signs and symptoms, including bone pain, back pain, leg weakness (from spinal cord and nerve-root compression), weight loss, anemia, or a generalized decline in performance status.

• The most common site of metastases is in the bones, which often results in bone pain, spinal cord compression, and anemia.

Comments
• Most patients who are diagnosed with prostate cancer have no clinical symptoms related to their cancer; however, a small proportion of patients do have symptoms of metastatic disease at presentation.

• The serum PSA level at the time of diagnosis of prostate cancer carries important prognostic information. A highly elevated PSA level in a man with metastatic cancer of unknown primary strongly suggests a prostatic origin of the cancer.

3.5 Refer men with an elevated or rapidly rising PSA level for a transrectal ultrasonography-guided prostate biopsy regardless of other symptoms.

Recommendations
• If the PSA level is >4.0 ng/mL, refer the patient to a urologist for consideration of a TRUS-guided prostate biopsy.

• If an elevated PSA level is detected at a time when the patient has clinical signs or symptoms of prostatitis, treat the prostatitis and recheck the PSA level 4 to 8 weeks later.

• If the PSA level is <4.0 ng/mL but is rising at a rate >0.75 ng/mL per year as determined by at least three separate measurements at least 18 months apart, consider referring the patient to a urologist for a TRUS-guided prostate biopsy.

• **High-value care:** Do not refer patients for prostate biopsy if they would not undergo treatment for a diagnosed cancer.

• See table [Laboratory and Other Studies for Prostate Cancer](#).

Evidence
• A 2013 guideline from the European Society of Medical Oncology recommended using PSA, prostate size on exam, and other factors to determine the need for biopsy and recommended transrectal-ultrasound biopsy for men undergoing biopsy (39).

• A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer stated that PSA alone should not automatically lead to a prostate biopsy, but stressed the importance of considering all clinical factors and engaging in shared decision-making.

• A cross-sectional study evaluated the accuracy of PSA, DRE, and transrectal ultrasound for the diagnosis of prostate cancer in 1001 men who underwent prostate biopsy. Overall, 25% of participants were diagnosed with prostate cancer. PSA was overall the best test. The sensitivity of hypoechoic findings on ultrasound was approximately 62% (43).

• A retrospective study evaluated the sensitivity of different screening tests in 50 African-American men newly diagnosed with prostate cancer. Overall, 94% had elevated PSA, 60% had findings on DRE, and 78% had an abnormal transrectal ultrasound (44).

• The Baltimore Longitudinal Study of Aging, which followed men for more than 7 years, reported that a PSA velocity >0.75 ng/mL per year had an 80% sensitivity and a 66% specificity for predicting prostate cancer. Among men with a PSA level between 4.0 and 10.0 ng/mL, a PSA velocity >0.75 ng/mL per year had a specificity of 95%. For men with a rising PSA level between 2.0 and 4.0 ng/mL checked on at least three occasions over a period of at least 18 months, a PSA velocity of >0.1 ng/mL per year had a sensitivity of 81% and a specificity of 50% (45; 46).
• A 2001 narrative review noted that in men who have biopsies after screening, about 25% of those with a PSA level between 4.0 and 10.0 ng/mL will be found to have prostate cancer, and more than 50% of those with a PSA level >10.0 ng/mL will be found to have prostate cancer (47).

Rationale
• Pathologic diagnosis is mandatory for prostate cancer and can be accomplished by a relatively simple office procedure.
• An elevated or rapidly rising PSA level can indicate the presence of prostate cancer, but the utility of calculating PSA velocity has not been shown.

Comments
• Accurate assessment of PSA velocity requires obtaining at least three measurements, at least 18 months apart, and prospective studies have not confirmed the utility of calculating PSA velocity as part of a screening strategy.

3.6 Refer men with a nodule or abnormal firmness on digital rectal examination for a transrectal ultrasonography-guided prostate biopsy.

Recommendations
• Refer men with a palpable prostate nodule or prostate induration detected on DRE for a TRUS-guided prostate biopsy.
• Measure their serum PSA level before the biopsy.
• Give antibiotic prophylaxis with a quinolone before biopsy.
• See table Laboratory and Other Studies for Prostate Cancer.

Evidence
• A 2013 guideline from the European Society of Medical Oncology recommended that prostate biopsies be carried out under guidance of transrectal ultrasound (39).
• A 2007 systematic review evaluated the diagnostic accuracy of extended and saturation prostate biopsy. Overall, the optimal biopsy strategy was found to include six standard “sextant” biopsies plus up to 12 additional core biopsies laterally to the base and medially to the apex (48).
• A 2011 Cochrane review of antibiotic prophylaxis for prostate biopsy included 19 studies with 3599 patients. Compared to no antibiotics, antibiotic therapy led to lower rates of bacteremia (RR, 0.67 [CI, 0.49 to 0.92]), urinary tract infection (RR, 0.37 [CI, 0.22 to 0.62]), and hospitalization (RR, 0.13 [CI, 0.03 to 0.55]). Quinolones were the most often studied antibiotics. Duration of treatment and number of doses (single vs. multiple) were not clearly related to variable outcomes (49).
• A prospective study evaluated the diagnostic accuracy of different numbers of samples in 512 men undergoing prostate biopsy for suspected cancer. All patients had 8 to 10 standard biopsies plus additional biopsies. The sensitivity of the standard sextant approach was 85%; a combination of the standard approach plus additional targeted biopsies based on ultrasound findings had sensitivity of 93% to 98% (50).

Rationale
• A palpable prostate nodule may represent a clinically significant cancer and should be investigated further.
• A prebiopsy PSA level should be obtained to help assess the prognosis if the biopsy specimen shows cancer.

Comments
• Biopsy is the accepted method for establishing the diagnosis.
3.7 Consider repeating the prostate biopsy if the initial result is not definitive.

Recommendations

- Repeat the prostate biopsy in men who are found to have high-grade prostatic intraepithelial neoplasia but no cancer.
- Consider repeating the prostate biopsy in any man whose initial biopsy result does not reveal prostate cancer if six or fewer areas of the prostate were sampled.
- Optimal timing of a repeat biopsy in patients with high-grade prostatic intraepithelial neoplasia or initial negative biopsies and six or fewer biopsies is unknown but should be considered within 6 to 12 months.
- Consider saturation or extended biopsy (at least 20 biopsy cores) in men with persistent suspicion for prostate cancer and repeated negative biopsies.
- See table Laboratory and Other Studies for Prostate Cancer.

Evidence

- A 2007 systematic review evaluated the diagnostic accuracy of extended and saturation prostate biopsy. Overall, the optimal biopsy strategy was found to include six standard “sextant” biopsies plus up to 12 additional core biopsies laterally to the base and medially to the apex (48).
- A prospective study evaluated predictors of prostate cancer on repeat biopsies in 1051 men with PSA between 4.0 ng/mL and 10.0 ng/mL. All patients were initially biopsied, then the 820 men with a negative biopsy underwent repeat biopsy 6 weeks later. Prostate cancer was found in 10% of men who underwent repeat biopsy (51).
- A cross-sectional study evaluated the sensitivity of the standard sextant prostate biopsy compared with prostate biopsy with additional samples in 119 patients who underwent extensive biopsy. Forty-eight patients had prostate cancer, among whom 35% had cancer only in the additional biopsy regions (52).
- In a study of 224 men with elevated PSA and initially negative biopsies with 1.8 sextant biopsy sessions, repeat saturation biopsy (mean of 23 biopsy cores) detected cancer in 34% of the study subjects (53).
- A study of 161 men with persistently elevated PSA level (median, 9.0 ng/mL) and at least two previously negative 8-core biopsies found that saturation biopsy (average of 24 biopsy cores) detected prostate cancer in 41% of subjects (54).

Rationale

- Standard sextant prostate biopsies (sampling the apex, base, and mid-zone of the left and right sides of the prostate) have been clearly shown to have high false-negative rates.
- High-grade prostatic intraepithelial neoplasia is associated with an increased risk for prostate cancer.

3.8 Perform staging evaluation to exclude regional or metastatic disease in select patients with biopsy-confirmed prostate cancer.

Recommendations

- Classify the stage of disease in all patients diagnosed with prostate cancer using the TNM staging system.
- Obtain a bone scan in patients with any of the following:
  - Clinical stage T1 and PSA level >20.0 ng/mL
  - Clinical stage T2 and PSA level >10.0 ng/mL
- Gleason sum ≥8
- Clinical stage T3 or T4
- Clinical symptoms
- Obtain a pelvic MRI or CT scan in patients with clinical stage T3 or T4 and in patients with clinical stage T1 or T2 and a greater than 20% probability of lymph-node involvement.
- **High-value care:** Do not perform further radiographic testing in other patients unless they have signs or symptoms suggesting metastatic disease.
- See table [Laboratory and Other Studies for Prostate Cancer](#).
- See table [TNM Staging Classification of Prostate Cancer](#).

### Evidence

- A 2013 [guideline](#) from the European Society of Medical Oncology staging of prostate cancer using MRI (39).
- The 2009 AUA best practice [statement](#) update on PSA testing stated that bone scans are not indicated in asymptomatic men with clinically localized prostate cancers unless the PSA level is ≥20.0 ng/mL. The statement did not recommend CT scans in men with clinically localized prostate cancer unless the PSA level is ≥25.0 ng/mL (55).
- A 2014 NICE (UK) [guideline](#) on the diagnosis and treatment of prostate cancer recommended against imaging in patients who will not receive radical therapy. The guideline recommended that men with high-risk localized or locally invasive prostate cancer undergo pelvic imaging with MRI, using CT if MRI is contraindicated. The guideline recommended against CT and bone scan for patient with low- or intermediate-risk localized prostate cancer.
- A 2002 systematic review of the accuracy of MRI for prostate cancer staging included 71 articles and five abstracts, comprising 146 comparisons. Risk for bias was overall high. For overall prostate cancer staging, the pooled maximal sensitivity and specificity were 71%; using a cutoff that resulted in a specificity of 95% resulted in a sensitivity of only 29%. For invasion of seminal vesicles, the pooled maximal sensitivity and specificity were 82%, and for extracapular extension, the pooled maximal sensitivity and specificity were 64% (56).
- A prospective study evaluated the ability of MRI, with or without injection of lymphotropic superparamagnetic nanoparticles, to detect lymph node metastases in 80 patients with newly diagnosed prostate cancer without clinical evidence of metastatic disease. MRI findings were compared with a reference standard of lymph node resection or biopsy. Analyzed at the level of the lymph node, the sensitivity of standard MRI was 35.4% and the sensitivity of MRI with lymphotropic superparamagnetic nanoparticles was 90.5% (P<0.001) (57).
- A prospective, population-based study of 3690 men with newly diagnosed prostate cancer reported that patients with a PSA level <20.0 ng/mL and a Gleason sum <8 had a 98.6% chance of having a negative bone-scan result and a 97.3% chance of having a negative CT-scan result (58).
- A retrospective study determined factors associated with positive bone scans among 631 consecutive men with newly diagnosed prostate cancer. Among patients with a PSA level of <50.0 ng/mL, Gleason sum of <8, and a clinical stage of <T2c, only 3 of 308 men (1%) had a positive bone-scan result, and only 2 of 311 (0.6%) had a positive CT-scan result. Independent predictors of a positive bone scan included PSA >50 (OR, 5.25 [CI, 3.43 to 8.04] compared with PSA 0 to 15) and Gleason score (OR, 2.25 [CI, 1.43 to 3.54]) (59).
- A retrospective study evaluated bone scan findings in 683 men who were newly diagnosed with prostate cancer. Positive bone-scan results were seen in 0 of 290 (0%) men with a PSA level <10.0 ng/mL, 4 of 88 (4.5%) men with a PSA level between 10.0 and 20.0 ng/mL, and 24 of 112 (21%) with a PSA level >20.0 ng/mL (60).
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- A retrospective study evaluated the correlation between PSA values and bone-scan results in 2064 men with newly diagnosed prostate cancer and PSA <20 ng/mL. Overall, 1.2% of patients had an abnormal bone scan. Among 561 men with a PSA level <10.0 ng/mL, 3 (0.5%) had a positive bone scan (61).

- A 2014 narrative review described predictors of the risk for bone metastases in patients with prostate cancer (62).

Rationale
- Patients with metastatic disease should not receive local therapy with surgery or radiation.
- Patients with high PSA values or poorly differentiated disease have a significant incidence of radiologically detectable distant metastases, occurring most often in bone and pelvic lymph nodes.
- Patients with favorable prognostic signs (stage T1 and PSA level ≤20.0 ng/mL, stage T2 and PSA level ≤10.0 ng/mL, and Gleason score <8) are extremely unlikely to have metastases detected by bone, CT, or MRI scan, and false-positive results in this population are not uncommon.

Comments
- The NCCN has issued guidelines for the management of prostate cancer, which are available for clinical use on their web site.
- Newer staging tests, including endorectal MRI and ProstaScint, do not have an established role in prostate cancer.

3.9 Consider the broad differential diagnosis of localized and metastatic prostate cancer.

Recommendations
- Consider benign prostatic hyperplasia and prostatitis in the differential diagnosis in patients with an elevated serum PSA or obstructive urinary symptoms.
- Consider measuring free PSA (also known as PSA II) to help in distinguishing prostate cancer from BPH or prostatitis in patients with a serum PSA level between 4.0 and 10.0 ng/mL and whose initial prostate biopsy specimens show only benign prostatic tissue.
- Consider other neoplastic and inflammatory disease processes presenting with lymphadenopathy, bony lesions, or both.
- See table Differential Diagnosis of Prostate Cancer.

Evidence
- A 2005 systematic review of diagnostic accuracy of the ratio of free to total PSA or complexed PSA for prostate cancer in men with intermediate levels of PSA (2 to 10 ng/mL) included 61 studies. For the ratio of free to total PSA, sensitivity and specificity varied based on the cutoff value, ranging from a sensitivity of 50% and specificity of 80% at a cutoff of 0.10 and a sensitivity of 95% and specificity of 18% at a cutoff of 0.25 (63).
- Mainly consensus.

Rationale
- The lack of specificity of serum PSA elevations for prostate cancer can cause confusion when the initial set of biopsy specimens shows only benign tissue.
- Men with prostate cancer tend to have a higher percentage of their serum PSA protein bound and a lower percentage free compared with men without prostate cancer; however, an optimal cutoff point for percentage free PSA has not been clearly identified.

Comments
• The utility of measuring serum free PSA in order to distinguish between cancer and other causes of an elevated serum total PSA has not been prospectively validated.
4. Consultation

Consult a urologist for evaluation of a palpable prostate abnormality or an elevated PSA level. Depending on the stage of the patient's disease, refer patients with prostate cancer to a urologist, radiation oncologist, or medical oncologist.

4.1 Refer patients with a palpable prostate abnormality to a urologist for further evaluation.

Recommendations
- In the context of a decision to pursue screening or in the setting of urinary symptoms, refer a patient with a palpable abnormality of the prostate to a urologist for evaluation, regardless of whether a PSA level has been obtained and regardless of whether it is normal or elevated.
- Defer transrectal ultrasonography because it will be used to guide the biopsy.

Evidence
- Consensus.

Rationale
- The presence of a palpable nodule on digital rectal examination may indicate a prostate cancer.
- Further radiologic evaluation, including TRUS, should be deferred because it cannot definitively exclude cancer and is usually done to guide prostate needle biopsies.

Comments
- Drawing a serum PSA level in this setting may be helpful but should not preclude further evaluation by a urologist, because some prostate cancers may be present as a nodule, despite low PSA levels.

4.2 Refer a patient with an elevated or rapidly increasing PSA level to a urologist if he is a potential candidate for therapy.

Recommendations
- In the context of a decision to pursue screening or in the setting of urinary symptoms, refer a patient with an elevated serum PSA level who does not appear to have prostatitis to a urologist for a transrectal ultrasonography-guided biopsy (and staging, if positive).
- Do not refer patients who have a short life expectancy that would be unlikely to be affected by prostate cancer or who would refuse treatment for prostate cancer if diagnosed.

Evidence
- A 2013 guideline from the European Society of Medical Oncology recommended using PSA, prostate size on exam, and other factors to determine the need for biopsy and recommended transrectal-ultrasound biopsy for men undergoing biopsy (39).
- A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer stated that PSA alone should not automatically lead to a prostate biopsy, but stressed the importance of considering all clinical factors and engaging in shared decision-making.
- A cross-sectional study evaluated the accuracy of PSA, DRE, and transrectal ultrasound for the diagnosis of prostate cancer in 1001 men who underwent prostate biopsy. Overall, 25% of participants were diagnosed with prostate cancer. PSA was overall the best test. The sensitivity of hypoechoic findings on ultrasound was approximately 62% (43).
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- A retrospective study evaluated the sensitivity of different screening tests in 50 African-American men newly diagnosed with prostate cancer. Overall, 94% had elevated PSA, 60% had findings on DRE, and 78% had an abnormal transrectal ultrasound (44).

- The Baltimore Longitudinal Study of Aging, which followed men for more than 7 years, reported that a PSA velocity >0.75 ng/mL per year had an 80% sensitivity and a 66% specificity for predicting prostate cancer. Among men with a PSA level between 4.0 and 10.0 ng/mL, a PSA velocity >0.75 ng/mL per year had a specificity of 95%. For men with a rising PSA level between 2.0 and 4.0 ng/mL checked on at least three occasions over a period of at least 18 months, a PSA velocity of >0.1 ng/mL per year had a sensitivity of 81% and a specificity of 50% (45; 46).

- A 2001 narrative review noted that in men who have biopsies after screening, about 25% of those with a PSA level between 4.0 and 10.0 ng/mL will be found to have prostate cancer, and more than 50% of those with a PSA level >10.0 ng/mL will be found to have prostate cancer (47).

Rationale

- An elevated serum PSA level is associated with prostate cancer, prostatitis, and benign prostatic hyperplasia.

- If a PSA test has been performed and the result is elevated above the normal range for that person's age, and if there is no other apparent cause (benign prostatic hyperplasia, prostatitis) for the findings, it is possible the patient has prostate cancer.

Comments

- No uniform standards exist for what constitutes an elevated PSA level; however, most standard PSA assays use 4.0 ng/mL as a cutoff for normal. Age-specific standards may be more appropriate but have not been validated.

4.3 Consult a urologist for help in managing surgically approachable prostate cancer.

Recommendations

- Refer patients with prostate cancer to a urologist for:
  - Prostate biopsy
  - Radical prostatectomy
  - Bladder obstruction
  - Complications of surgery

Evidence

- Consensus.

Rationale

- Radical prostatectomy is a difficult and complicated operation.

- Urologists specialize in operating on the genitourinary system, and they are the physicians who are best qualified to do prostate biopsies and radical prostatectomies.

4.4 Refer patients who may benefit from radiation therapy to a radiation oncologist.

Recommendations

- Refer patients to a radiation oncologist if they have:
  - Localized or locally advanced prostate cancer to determine whether radiation therapy represents a good treatment option
  - Symptomatic metastatic prostate cancer (refer as needed)
- Brain or other central nervous system metastases

**Evidence**
- Consensus.

**Rationale**
- Radiation oncologists are fully and specifically trained to treat prostate cancer by administering external-beam radiation or brachytherapy.
- Radiation therapy can be used as potentially curative therapy for localized disease or to relieve pain and certain other symptoms caused by advanced disease.
- CNS metastases are generally treated with radiation, surgery, or both.

**Comments**
- Brachytherapy is sometimes administered by a urologist working together with a radiation oncologist.

4.5 **Refer patients with prostate cancer to a medical oncologist.**

**Recommendations**
- Refer patients to a medical oncologist if they have:
  - Localized or locally advanced prostate cancer to discuss medical treatment options
  - Metastatic prostate cancer or a rising PSA level following local therapy
  - Castration-resistant prostate cancer to be evaluated for chemotherapy and other systemic treatments

**Evidence**
- Research has shown that when advising men with localized prostate cancer, radiation oncologists are more likely to recommend radiation therapy, whereas urologists are more likely to recommend surgery (171 [10866869]).

**Rationale**
- Medical oncologists are specially trained in the use of chemotherapy, hormonal therapy, and other systemic treatments for cancer.
- The treatment of metastatic prostate cancer has become more complex over the past decade, and a specialist can aid in decisions about when to use hormonal therapy, when to use chemotherapy, and which agents to use.

4.6 **Refer patients with metastatic hormone-refractory disease to a palliative care specialist.**

**Recommendations**
- Refer patients with refractory metastatic disease for palliative care.
- Note that palliative care will help ensure the patient's comfort.
- Note that palliative care can be delivered in conjunction with more aggressive care to prolong survival.

**Evidence**
- A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended that men with metastatic prostate cancer be offered access to palliative care teams.

**Rationale**
- Early palliative care can improve quality of life and reduce mortality.
- A 2007 narrative review discussed palliative care of advanced prostate cancer (64).
5. Hospitalization

Consider hospitalizing patients with advanced prostate cancer for management of symptoms related to bone metastases. 

5.1 Consider hospitalizing patients who suffer from intractable pain from advanced prostate cancer. 

Recommendations
- Admit patients for acute pain control if they are suffering from severe pain that is unresponsive to outpatient pain medication.

Evidence
- Consensus.

Rationale
- Advanced-stage (locally advanced or metastatic) prostate cancer can be extremely painful.
  - Patients are often undermedicated for their pain
  - A short hospital stay, during which pain medications are optimized, can often stabilize patients with pain that is otherwise difficult to control
  - Although most patients do not require hospitalization, it should be considered if pain is severe or remains intractable.
  - See module Pain.

Comments
- Often patient-controlled intravenous or epidural analgesics are useful in achieving adequate intravenous pain relief. Once the patient’s pain is under control, conversion to oral or transdermal pain-control modalities is possible (65).

5.2 Hospitalize or rapidly evaluate patients with prostate cancer who develop back pain and new neurologic symptoms and signs. 

Recommendations
- Prioritize patients for urgent evaluation to look for spinal cord or nerve-root compression in the presence of:
  - Back pain
  - New leg or arm weakness or numbness
  - Loss of perineal sensation
  - Loss of rectal tone
  - Acute urinary obstruction/urinary incontinence
- Refer any prostate cancer patient with unexplained back pain or neurologic deficits that might be due to epidural metastatic disease for an emergent MRI of the spine.
- Admit or rapidly evaluate patients with a suspected spinal cord compression or cauda equina compression (particularly those with any neurologic deficits) for high-dose or moderate-dose corticosteroids and consultation with a radiation oncologist and a neurosurgeon.
- Treat patients with neurologic deficits that may be due to epidural disease with one of the following regimens:
  - Dexamethasone, 96 g intravenous bolus, followed by 24 mg orally four times daily for 3 days, followed by a 10-day taper (high dose)
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- Dexamethasone, 10 mg intravenous bolus, followed by 4 mg orally four times daily for 3 days, followed by taper over 2 weeks (moderate dose)
- Consult a radiation oncologist and a neurosurgeon emergently if spinal cord or cauda equina compression is seen on MRI or if neurologic deficits are present and are attributed to cord compression.
- Do not withhold aggressive therapy for spinal cord compression just because severe neurologic deficits have already developed.

Evidence

- A randomized trial compared high-dose dexamethasone, 96 mg/d given as 24 mg four times daily, to no corticosteroids in 57 patients with carcinomatous metastatic spinal cord compression undergoing radiation therapy. More patients in the dexamethasone group than in the control group survived with gait function (P=0.046), with an NNT of 20 (P=0.046). Six months after treatment, more patients in the dexamethasone group were ambulatory (59% compared with 33% in the control group; NNT=4). No difference in survival was seen. Three of 27 (11%) patients receiving dexamethasone had serious complications consisting of one case each of a perforated gastric ulcer requiring surgery, hypomania, and psychosis (66).

- A randomized, controlled trial of patients with metastatic cord compression receiving treatment with moderate-dose dexamethasone compared a high-dose bolus (96 mg) with a moderate-dose bolus (10 mg) and found no differences in pain or neurologic function between the two treatment arms (67).

- A retrospective case series of 28 patients receiving high-dose dexamethasone reported that 4 (14.3%) suffered serious side effects, including fatal upper-GI bleeding, rectal bleeding requiring transfusion, gastrointestinal perforation, and perforation of the sigmoid colon. The subsequent 38 patients were treated with moderate-dose dexamethasone, 4 mg orally every 6 hours, and no serious side effects were seen (P <0.03 for the difference in rate of serious side effects) (68).

- A retrospective analysis of patients with metastatic spinal cord compression showed that patients treated with emergency surgery rather than elective surgery had a substantially higher rate of improvement in neurologic function (61% vs. 25%) (69).

- A small, randomized study of patients with spinal cord compression from metastases showed that the combination of surgical resection followed by radiation was superior to radiation alone, with all patients in this study receiving high-dose dexamethasone (100 mg followed by 24 mg every 6 hours until surgery). With the combined approach, a higher proportion of patients were ambulatory (84%) compared with the radiation-alone group (57%; P=0.001) (70).

Rationale

- Back pain with neurologic deficits in a patient with prostate cancer is an oncologic emergency, and should be considered due to metastatic disease and possible spinal cord compression until proven otherwise.
- A spinal MRI is the best imaging modality to adequately visualize the epidural space and evaluate for spinal cord compression.
- Immediate intervention in spinal cord compression is necessary to prevent permanent neurologic deficits, including paralysis and incontinence.
- Corticosteroids can reduce the vasogenic edema that occurs early in the course of cord compression and thus can reduce the pressure on nerves, relieve pain, and temporarily reverse early neurologic deficits; however, definitive treatment requires surgical resection or radiation therapy and should be provided urgently or emergently, depending on the severity of the findings on MRI and neurologic examination.
Although it is sometimes believed that patients with spinal cord compression who have moderate-to-severe weakness will never recover their strength, many cases of dramatic recovery of function have been reported with aggressive therapy.

**Comments**
- Use of dexamethasone, 96 mg/d, is controversial because of the potential for such treatment to result in GI bleeding and severe mental status changes; however, the best evidence showing that corticosteroid use can reverse neurologic deficits comes from trials using this dose. It is more common to use the moderate dosing schedule.
- In appropriate patients, high-dose glucocorticoids combined with surgical decompression and radiation leads to better results than observed with radiation and glucocorticoids.
6. Therapy

Consider several non-drug treatment options for patients with prostate cancer, including radical prostatectomy, external-beam radiation therapy, brachytherapy, and watchful waiting or active surveillance; and consider androgen deprivation therapy as the mainstay of treatment for advanced prostate cancer. [B] 

6.1 Discuss with appropriate specialists the referral of patients with clinically localized prostate cancer for consideration of treatment options. [C]

Recommendations

- For patients diagnosed with clinically localized prostate cancer, discuss the plan of care with a multidisciplinary group of physicians, including a urologist, radiation oncologist, and medical oncologist.

- Note that treatment options include
  - Watchful waiting
  - Active surveillance
  - Prostatectomy
  - External-beam radiation therapy
  - Brachytherapy
  - Hormonal therapy

Evidence

- A survey of urologists and radiation oncologists reported that, for men with moderately differentiated, clinically localized cancers and a life expectancy of 10 or more years, 93% of urologists recommended radical prostatectomy, whereas 72% of radiation oncologists believed surgery and external-beam radiotherapy were equivalent treatments. For most tumor grades and PSA levels, each group tended to preferentially recommend the treatment that it provided (71).

Rationale

- Localized prostate cancer can be managed in a variety of ways; there is no definitive evidence that one of these approaches is better than the others for men with low-risk disease.

- Physicians tend to recommend the treatment they are trained to provide over treatments other specialists provide, and meeting with a multidisciplinary group allows the patient to hear different perspectives on treatment.

6.2 Consider watchful waiting or active surveillance in men with low-risk or localized disease, particularly in men with limited life expectancy. [B]

Recommendations

- In men with low-risk disease, discuss active surveillance, which involves periodic clinical monitoring with curative intervention triggered by signs of disease progression.

- Note that active surveillance involves:
  - Measuring PSA every 3 to 4 months in the first year, with the interval lengthening to every 6 months after 3 or 4 years
  - Monitoring PSA velocity
  - Performing digital rectal exams every 6 months
Evidence

- A 2013 guideline from the European Society of Medical Oncology stated that observation should be discussed as an option for men with low-risk disease or those with intermediate-risk disease who are not suitable for aggressive therapy (39).
- A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended active surveillance as an option for men with low- or intermediate-risk prostate cancer and described a protocol for active surveillance.
- A 2007 guideline from the American Urological Association recommended radical prostatectomy, external-beam radiation therapy, active surveillance, and brachytherapy as treatment options for patients with clinically localized low-risk prostate cancer, and recommended discussing treatment side effects with patients (72).
- A 2012 systematic review of active surveillance for early-stage prostate cancer found wide variation in methods of active surveillance and noted that in many studies active surveillance could not be differentiated from watchful waiting. Overall, there was insufficient evidence to assess its effectiveness (73).
- A 2011 systematic review of treatments for localized prostate cancer for the U.S. Preventive Services Task Force included two randomized trials and nine cohort studies evaluating benefits and two randomized trials, 14 cohort studies, and 11 other studies evaluating harms. There was benefit to prostatectomy compared with watchful waiting in one randomized trial and eight cohort studies, with an NNT of 15 for all-cause mortality after 15 years in the randomized trial and a hazard ratio for all-cause mortality in observational data ranging from 0.41 to 0.50. Cohort studies showed mortality benefit to radiation therapy compared with watchful waiting (median adjusted HR, 0.68 [CI, 0.62 to 0.81]). Harms were estimated mostly from cohort studies; there was an additional patient with erectile dysfunction for every three men treated with prostatectomy, seven men treated with radiation therapy, or two to three men treated with androgen deprivation therapy, and one additional patient with urinary incontinence for every five men treated with prostatectomy (74).
- A 2010 Cochrane review of watchful waiting vs. radical prostatectomy for prostate cancer included only two studies, both of which predated widespread screening with PSA and one of which was of poor quality. After 15 years of follow-up, overall mortality did not differ between the groups (HR, 0.90 [CI, 0.56 to 1.43]) (75).
- A 2012 randomized trial, The Prostate Cancer Intervention Versus Observation Trial, compared radical prostatectomy to observation in patients with localized prostate cancer (mean age, 67). After a median follow-up time of 10 years, mortality was 47.0% in the radical prostatectomy group and 49.9% in the observation group (P=0.22). In subgroup analysis, radical prostatectomy resulted in lower mortality among patients with PSA >10 ng/mL (76).
- The U.S. Agency for Healthcare Research and Quality published in 2010 a study of the relative effectiveness and benefits of radiation treatment compared with no treatment for initial therapy for localized prostate cancer. Despite the inclusion of 62 randomized, controlled trials and nonrandomized direct comparative studies, the data were deemed insufficient to draw conclusions about differences between the two approaches.
- Cohort studies have found that, in men managed with watchful waiting, 15-year disease-specific survival was 80% (ranging from 95% for well-differentiated tumors to 30% for poorly differentiated tumors (77; 78; 79).
- A prospective cohort study initiated in November 1995 evaluated outcomes associated with active surveillance. PSA was assessed every 3 months for 2 years and then every 6 months in stable patients; a confirming biopsy was done 6 to 12 months after initial biopsy and then every 3 to 4 years until the patient was 80 years of age. Definitive therapy was recommended if there was a notable shortening of the PSA doubling time, histologic upgrade on repeat biopsy, or clinical
progression. Initially, men meeting favorable-risk criteria (Gleason sum ≤6, PSA level ≤10.0 ng/mL) and men over age 70 with a PSA level ≤15.0 ng/mL or a Gleason sum of ≤7 were eligible, and PSA doubling time of 2 years was used as a trigger for intervention. In 1999, PSA doubling time was changed to 3 years, and beginning January 2000, men of all ages had to meet favorable-risk criteria to be eligible. Updated data from this study, based on 450 men with favorable-risk disease followed for a median of 6.8 years, showed an overall survival of 78.6% and a 10-year prostate cancer-specific survival rate of 97.2%. The hazard ratio for death from another cause to death from prostate cancer was 18.6 at 10 years (80).

- A prospective cohort study of active surveillance, initiated in January 1995 at Johns Hopkins University, has reported findings for 769 men followed for a median of 2.7 years. Criteria for surveillance included clinical stage T1c, PSA density <0.15 ng/mL, Gleason sum ≤6, not more than two biopsy cores with cancer, and 50% or less prostate cancer involvement of any single positive core. The cohort was followed with twice-yearly PSA measurements (total and free) plus DRE and annual prostate biopsy (12 to 14 cores). Criteria for transition to intervention were Gleason sum >6, more than two biopsy cores with cancer, or more than 50% involvement of any core. Median survival free of intervention (the primary outcome) was 6.5 years after diagnosis, with 81%, 59%, and 41% of men in the surveillance cohort remaining free of intervention after 2, 5, and 10 years, respectively, of follow-up (81).

- A 2013 cost-effectiveness analysis evaluated the cost-effectiveness of observation compared with initial therapy in men with low-risk prostate cancer. In the base-case analysis of men aged 65, observation was more effective and less costly than therapy, and among initial therapies, brachytherapy was the most effective and least costly. The analysis was sensitive to the impact of therapies on mortality and other factors (82).

- A 2010 decision analysis assessed the effectiveness of active surveillance compared with initial definitive treatment for prostate cancer, using a hypothetical cohort of 65-year-old men with newly diagnosed, localized, and low-risk prostate cancer (PSA level <10.0 ng/mL, clinical stage ≤T2a disease, Gleason sum ≤6). The quality-adjusted life expectancy was greatest with active surveillance, followed by brachytherapy, intensity-modulated radiation therapy, and radical prostatectomy (83).

**Rationale**

- Because some prostate cancers grow slowly (sometimes over decades) and occur in older men with competing risks for mortality, deferral of active therapy may be a reasonable alternative to local treatment, in particular given the risks to quality of life with prostate surgery or radiation.

- An active-surveillance approach uses regular reassessment for progression or initial understaging with repeat prostate biopsy and PSA assessment, allowing for escalation to active therapy with a change in risk assessment.

**Comments**

- Watchful waiting is accompanied by issues that are poorly studied, including anxiety about a rising PSA level and risk of local symptoms from cancer.

**6.3 Consider radical prostatectomy for younger patients who have early-stage disease and a life expectancy of 10 or more years.**

**Recommendations**

- Consider recommending radical prostatectomy for patients who have clinical stage T1 or T2 disease, are younger than age 65, and have a life expectancy of 10 or more years.

- Be aware that the higher the serum PSA level and the higher the Gleason sum, the more likely it is that the patient will relapse after radical prostatectomy.
• Discuss the risk for erectile dysfunction (60% to 90%), urinary incontinence (7% to 54%), and perioperative complications with patients considering radical prostatectomy.

**Evidence**

• A 2013 guideline from the European Society of Medical Oncology stated that options for patients with intermediate-risk prostate cancer include radical prostatectomy, external-beam radiation with androgen deprivation therapy, or high-dose brachytherapy (39).

• A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended offering radical prostatectomy and radical radiotherapy as options for men with high-risk localized disease, in whom long-term disease control seems likely.

• A 2007 guideline from the American Urological Association recommended radical prostatectomy, external-beam radiation therapy, active surveillance, and brachytherapy as treatment options for patients with clinically localized low-risk prostate cancer, and recommended discussing treatment side effects with patients (72).

• A 2010 Cochrane review of watchful waiting vs. radical prostatectomy for prostate cancer included only two studies, both of which predated widespread screening with PSA and one of which was of poor quality. After 15 years of follow-up, overall mortality did not differ between the groups (HR, 0.90 [CI, 0.56 to 1.43]) (75).

• A 2011 systematic review of treatments for localized prostate cancer for the U.S. Preventive Services Task Force included two randomized trials and nine cohort studies evaluating benefits and two randomized trials, 14 cohort studies, and 11 other studies evaluating harms. There was benefit to prostatectomy compared with watchful waiting in one randomized trial and eight cohort studies, with an NNT of 15 for all-cause mortality after 15 years in the randomized trial and a hazard ratio for all-cause mortality in observational data ranging from 0.41 to 0.50. Cohort studies showed mortality benefit to radiation therapy compared with watchful waiting (median adjusted HR, 0.68 [CI, 0.62 to 0.81]). Harms were estimated mostly from cohort studies; there was an additional patient with erectile dysfunction for every three men treated with prostatectomy, seven men treated with radiation therapy, or two to three men treated with androgen deprivation therapy, and one additional patient with urinary incontinence for every five men treated with prostatectomy (74).

• A 2012 randomized trial, The Prostate Cancer Intervention Versus Observation Trial, compared radical prostatectomy to observation in patients with localized prostate cancer (mean age, 67). After a median follow-up time of 10 years, mortality was 47.0% in the radical prostatectomy group and 49.9% in the observation group (P=0.22). The rate of prostate cancer death in the prostatectomy group was 5.8% compared with 8.4% in the watchful-waiting group (P=0.09). In subgroup analysis, radical prostatectomy resulted in lower mortality among patients with PSA >10 ng/mL (76).

• A multi-institutional study of 2758 patients with stage T1 and T2 prostatic cancers undergoing radical prostatectomy at eight different hospitals reported that T1 and T2 patients with Gleason sums ranging from 5 to 7 had 10-year disease-specific and metastasis-free survival of 80% and 68%, respectively, whereas the figures for patients with Gleason sums ranging from 8 to 10 were 77% and 52%, respectively (84).

• A Johns Hopkins study of 2402 men having radical prostatectomy with a mean follow-up of 6.4 years reported a 15-year relapse-free survival of 79%, although only 4.3% of the patients in this series had been followed for 15 years or longer (85).

• A prospective cohort study evaluated long-term functional outcomes in 1655 men in whom localized prostate cancer had been diagnosed between the ages of 55 and 74 years and who had undergone either surgery (1164 men) or radiotherapy (491 men); functional status was assessed at baseline and at 2, 5, and 15 years after diagnosis. Patients who underwent prostatectomy were more likely to have urinary incontinence at 2 (OR, 6.22 [CI, 1.92 to 20.29]) and 5 years (OR, 5.10
Recommendations

6.4 Consider external-beam radiation therapy to the prostate for patients with prostate cancer with no evidence of distant metastases and a life expectancy of 10 or more years and combine it with anti-androgen therapy for higher-risk patients.  

Evidence

A 2013 guideline from the European Society of Medical Oncology stated that options for patients with intermediate-risk prostate cancer include radical prostatectomy, external-beam radiation with androgen deprivation therapy, or high-dose brachytherapy (39).
• A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended offering radical prostatectomy and radical radiotherapy as options for men with high-risk localized disease, in whom long-term disease control seems likely. For men receiving external-beam radiation, the guideline recommended a conformational approach and the co-administration of hormonal therapy for 2 years in men with Gleason scores ≥8.

• A 2007 guideline from the American Urological Association recommended radical prostatectomy, external-beam radiation therapy, active surveillance, and brachytherapy as treatment options for patients with clinically localized low-risk prostate cancer, and recommended discussing treatment side effects with patients (72).

• A 2011 systematic review of radiation treatments for localized prostate cancer included 75 studies (10 randomized trials and 65 cohort studies). Specific regimens and comparators varied, but overall higher doses of external-beam radiation therapy were associated with higher rates of long-term control of cancer (87).

• A 2011 systematic review of treatments for localized prostate cancer for the U.S. Preventive Services Task Force included two randomized trials and nine cohort studies evaluating benefits and two randomized trials, 14 cohort studies, and 11 other studies evaluating harms. There was benefit to prostatectomy compared with watchful waiting in one randomized trial and eight cohort studies, with an NNT of 15 for all-cause mortality after 15 years in the randomized trial and an HR for all-cause mortality in observational data ranging from 0.41 to 0.50. Cohort studies showed mortality benefit to radiation therapy compared with watchful waiting (median adjusted HR, 0.68 [CI, 0.62 to 0.81]). Harms were estimated mostly from cohort studies; there was an additional patient with erectile dysfunction for every three men treated with prostatectomy, seven men treated with radiation therapy, or two to three men treated with androgen deprivation therapy, and one additional patient with urinary incontinence for every five men treated with prostatectomy (74).

• A randomized trial of 225 men compared equal-dose conventional with conformal radiation therapy and found a significant reduction in radiation proctitis and rectal bleeding in the group receiving conformal therapy (88).

• A randomized trial compared high-dose or low-dose radiation delivered by conformation techniques in 393 men with clinical stage T1b to T2b prostate cancer and a serum PSA <15.0 ng/mL. At a median follow-up of 8.9 years, the 10-year biochemical failure rate was 32.4% in the low-dose group and 16.7% in the high-dose group (P<0.0001), although overall survival rates between the two groups were the same. Grade ≥3 genitourinary toxicity rates were 2% in both groups (89).

• A randomized trial compared radiation therapy alone to radiation therapy plus 4 months of androgen deprivation therapy in 1979 subjects with T1b-T2b prostate cancer and a PSA level of <20.0 ng/mL. After a mean follow-up time of 9 years, prostate cancer mortality was lower in the androgen deprivation group (4% vs. 8%, P=0.001). Overall survival was higher in the androgen deprivation group (62%) than in the radiotherapy-alone group (57%, P=0.03). A stratified analysis found that most of this benefit occurred in intermediate-risk patients (90).

• A European study randomly assigned 875 patients with locally advanced prostate cancer (predominantly T3 lesions) to receive either hormonal therapy or hormonal therapy plus radiation therapy. Hormonal therapy consisted of androgen blockade (e.g., gonadotropin-releasing hormone agonist plus an anti-androgen) for 3 months followed by continuous monotherapy with flutamide, 250 mg orally three times a day. The majority of men received breast irradiation for gynecomastia, likely due to the anti-androgen. The cumulative incidence of overall mortality at 10 years was 39.4% in the hormone-only group compared with 29.6% in the combined-treatment group (P<0.004). Urinary, rectal, and sexual problems were slightly more common in patients receiving both hormonal and radiation therapies (91).

• A prospective cohort study evaluated side effects in 1201 men who were treated for early-stage prostate cancer with prostatectomy, external-beam radiation therapy, or brachytherapy. Two years after treatment, 35% of men who underwent prostatectomy, 37% of those who underwent external-beam radiotherapy,
and 43% of those who underwent brachytherapy were able to attain functional erections (92). One year after treatment, problems with urinary incontinence were reported by 24% of patients who underwent prostatectomy, 15% who underwent external-beam radiotherapy, and 15% of those who underwent brachytherapy (93).

- A prospective cohort study (the Spanish Multicentric Study of Clinically Localized Prostate Cancer) evaluated side effects over time in 435 men treated for prostate cancer with radical prostatectomy, external-beam radiotherapy, or brachytherapy. The mean change in EPIC score for sexual function in men undergoing conformal external-beam radiation therapy (from pretreatment to 3 years after treatment) was \(-10.6 \text{ (SD=22.4). Three years after external radiation therapy, 25% of men reported urinary incontinence adverse effects, 8% of men reported severe bowel problems, and 15% reported small to moderate bowel problems (94).}

- In an analysis of SEER data from 2000 to 2009 in patients with nonmetastatic prostate cancer rates of GI and urinary morbidity, erectile dysfunction, hip fractures, and additional cancer therapy were compared. Use of IMRT vs. conformal radiation therapy increased from 0.15% in 2000 to 95.9% in 2008. Among patients with nonmetastatic prostate cancer, the use of IMRT compared with conformal radiation therapy was associated with less GI morbidity and fewer hip fractures but more erectile dysfunction; IMRT compared with proton therapy was associated with less GI morbidity (95).

**Rationale**

- External-beam radiotherapy is noninvasive and has a different side-effect profile from radical prostatectomy.
- Treatment can be effective in curing organ-confined prostate cancer and locally advanced prostate cancer.
- There is no clear evidence that either surgery or radiation therapy is more effective in treating prostate cancer.
- Compared with radiation therapy alone, combined radiation and androgen deprivation is more effective in men with a Gleason sum >7 or clinical stage T3 or T4.
- Because patients with high-risk features benefit from combined radiation and hormonal therapy, it is surmised that intermediate-risk patients may benefit as well.

**Comments**

- Conformal radiation therapy permits escalation to doses that are not tolerated using conventional radiotherapy, and there is evidence that these higher doses may result in improved biochemical disease-free survival and metastasis-free survival.
- Only two randomized, controlled trials have compared radical prostatectomy with external-beam radiation therapy, but both were small and flawed, and neither trial is considered persuasive. Many single-institution series have shown excellent 10- and 15-year disease-specific survival rates with external-beam radiation therapy.
- There is a lack of good quality trials comparing radiation treatments to no treatment for localized prostate cancer.

**6.5 Consider brachytherapy in patients with localized low-risk disease and few or no obstructive symptoms.**

**Recommendations**

- Consider recommending radioactive seed implantation (brachytherapy) to men with no significant urinary obstructive symptoms and who have favorable-risk, clinically localized prostate cancer (PSA level <10.0 ng/mL, Gleason sum <7, and clinical stage T1c).
- Discuss the risk for erectile dysfunction (37%), urinary symptoms (16%), and bowel or rectal symptoms (8%) with patients considering brachytherapy.
- Note that patients with very large or small prostate volumes are not ideal candidates.
Evidence

- A 2013 guideline from the European Society of Medical Oncology stated that options for patients with intermediate-risk prostate cancer include radical prostatectomy, external-beam radiation with androgen deprivation therapy, or high-dose brachytherapy (39).

- A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended against brachytherapy alone for high-risk localized prostate cancer but recommended the combination of brachytherapy plus external beam radiotherapy as a treatment option.

- A 2007 guideline from the American Urological Association recommended radical prostatectomy, external-beam radiation therapy, active surveillance, and brachytherapy as treatment options for patients with clinically localized low-risk prostate cancer, and recommended discussing treatment side effects with patients (72).

- A 2011 systematic review of treatments for localized prostate cancer for the U.S. Preventive Services Task Force included two randomized trials and nine cohort studies evaluating benefits and two randomized trials, 14 cohort studies, and 11 other studies evaluating harms. There was benefit to prostatectomy compared with watchful waiting in one randomized trial and eight cohort studies, with an NNT of 15 for all-cause mortality after 15 years in the randomized trial and a hazard ratio for all-cause mortality in observational data ranging from 0.41 to 0.50. Cohort studies showed mortality benefit to radiation therapy compared with watchful waiting (median adjusted HR, 0.68 [CI, 0.62 to 0.81]). Harms were estimated mostly from cohort studies; there was an additional patient with erectile dysfunction for every three men treated with prostatectomy, seven men treated with radiation therapy, or two to three men treated with androgen deprivation therapy, and one additional patient with urinary incontinence for every five men treated with prostatectomy (74).

- A 2007 cohort study described long-term outcomes after treatment with brachytherapy in 2693 patients with T1-T2 prostate cancer from 11 institutions. All patients received permanent brachytherapy alone: 1831 (68%) with a median dose (144 Gy) of iodine-125 and 862 (32%) with a median dose (130 Gy) of palladium-103. After a mean follow-up time of 63 months, the 8-year PSA relapse-free survival for patients with low-risk, intermediate-risk, and high-risk disease was 82%, 70%, and 48%, respectively (P<0.001). Factors associated with long-term disease-free survival included tumor stage, Gleason sum, pretreatment PSA level, year of treatment, and postimplantation dosimetric quality (96).

- A cohort study reported outcomes in 229 patients with T1-T3 prostate cancer who received brachytherapy, among whom 82 were determined to be at high risk and received additional external-beam radiation therapy. After a median follow-up time of 10 years, the overall disease-free survival rate was 70%. Disease-free survival was 66% among patients who received brachytherapy alone and 79% among those who received brachytherapy and external-beam radiation therapy (97).

- A retrospective cohort study from the Seattle Prostate Institute described outcomes in 125 consecutive patients with stage T1-T2b prostate cancer who were treated with brachytherapy. Ten-year relapse-free survival was 85% and no patient had died of prostate cancer (98).

- A retrospective cohort study described outcomes in 809 patients with T1-T2a tumors treated with radiiodine seed implants; 276 patients had intermediate risk factors (Gleason sum of 7, PSA level of 10.0 to 15.0 ng/mL, or both). The overall 5-year survival rate among patients with intermediate risk factors was not different from that in the rest of the cohort (98%). The 5-year relapse-free survival rate was 97% in the traditional low-risk group vs. 94% in the 276 patients with intermediate risk factors. Lacking robust randomized data, the management of intermediate-risk patients with seed implants continues to be debated, but this large series suggests that some intermediate-risk patients may be acceptable candidates for seed implants (99).
• A prospective cohort study evaluated side effects in 1201 men who were treated for early-stage prostate cancer with prostatectomy, external-beam radiation therapy, or brachytherapy. Two years after treatment, 35% of men who underwent prostatectomy, 37% of those who underwent external-beam radiotherapy, and 43% of those who underwent brachytherapy were able to attain functional erections (92). One year after treatment, problems with urinary incontinence were reported by 24% of patients who underwent prostatectomy, 15% who underwent external-beam radiotherapy, and 15% of those who underwent brachytherapy (93).

• A prospective cohort study (the Spanish Multicentric Study of Clinically Localized Prostate Cancer) evaluated side effects over time in 435 men treated for prostate cancer with radical prostatectomy, external-beam radiotherapy, or brachytherapy. The mean change in EPIC score for sexual function in men undergoing brachytherapy (from pretreatment to 3 years after treatment) was −9.9 (SD=23.5) (94).

Rationale
• Local therapy can minimize side effects, but delivering adequate doses to prostate nodules presents a challenge because the nodules, by definition, protrude from the prostate, and surrounding a nodule with radioactive seeds is difficult.

Comments
• There are several potential advantages to seed-implant therapy, including possible benefits with regard to erectile dysfunction and exposure to surgical risks, as well as disadvantages, including rectal toxicity and urinary obstruction.
• Seed implants have become popular, driven primarily by concerns about the morbidity of surgery and external-beam radiation.
• Although most information regarding the use of seed implants has come from studies of low-risk patients, emerging data suggest that some intermediate-risk patients may be suitable candidates for this treatment as well.

6.6 Begin androgen deprivation therapy in patients who have a rising PSA level following therapy for localized disease or who are at high risk after prostatectomy.

Recommendations
• Monitor serum PSA in patients following local therapy for prostate cancer for the remainder of their lives, with a frequency dependent on the initial risk stratification and the patient's current health situation.
  • Consider starting ADT if the PSA level starts to rise from the post-treatment nadir
  • Consider intermittent androgen suppression for rising PSA after radiotherapy
  • Consider obtaining a bone scan and a CT scan of the abdomen and pelvis periodically if the PSA level continues to rise, particularly if the rate of rise increases
  • Consider immediate androgen deprivation therapy in men who are at high risk for progression after prostatectomy (e.g., with positive surgical margins or pT3 disease).
• See table Drug Treatment for Prostate Cancer.

Evidence
• A 2006 ASTRO consensus conference recommended that a rise by 2 ng/mL or more above the nadir PSA be considered the standard definition for biochemical failure after EBRT with or without HT (100).
• A 2013 guideline from the European Society of Medical Oncology on the management of prostate cancer recommended that patients with biochemical relapse receive androgen deprivation therapy
if they have a PSA doubling time <3 months, symptomatic local disease progression, or known metastatic disease (39).

- A randomized trial compared immediate androgen deprivation therapy with delayed therapy (at the time of recurrence or distant metastases) in 98 men with node-positive prostate cancer who had undergone radical prostatectomy. After a median follow-up time of 12 years, overall mortality (36% vs. 55%, P=0.04) and prostate-cancer mortality (15% vs. 49%, P=0.0004) were lower in the immediate-therapy group than in the delayed-therapy group (101).

- A randomized non-inferiority trial compared intermittent and continuous androgen deprivation therapy in 1386 patients with elevated PSA (>3 ng/mL) after radiotherapy for localized prostate cancer. After a median follow-up time of 6.9 years, overall mortality was similar in the intermittent-therapy (38.8%) and continuous-therapy (36.8%) groups (HR, 1.02 [CI, 0.86 to 1.21]), which met criteria for non-inferiority (102).

- A randomized trial compared immediate postoperative radiotherapy (60 Gy conventional irradiation delivered over 6 weeks) to surgery only (with “wait-and-see” radiotherapy) in 1005 men with a positive surgical margin or pT3 cancer. After a median follow-up time of 5 years, rates of biochemical progression-free survival were higher in the immediate-radiotherapy group (74.0%) than in the surgery-only group (52.6%), but mortality did not differ between the groups (103).

Rationale

- A rising PSA level after radical prostatectomy and a consistently rising PSA level after radiation therapy are generally interpreted as signifying relapse of the prostate cancer.

- It remains unclear whether to initiate ADT in such patients without radiologic evidence of metastatic disease.

Comments

- There is no evidence whether or not ADT is beneficial in treated patients with a rising PSA level but no radiographically evident metastases. Although many experts feel that it is preferable to start ADT before the appearance of metastases, no specific PSA level or rate of increase in PSA has been identified as an appropriate trigger for the initiation of such treatment. Other experts argue that there is no scientific justification for starting ADT before the radiologic documentation of metastatic disease; however, there is increasing evidence that earlier ADT may improve outcomes for certain groups of patients.

6.7 Administer adjuvant androgen deprivation therapy with external-beam radiation therapy for patients with high-risk localized or locally advanced prostate cancer.

Recommendations

- For patients who are having external-beam radiation for bulky or locally advanced prostate cancer (T3-T4 or pelvic lymph-node metastases):
  - Give androgen deprivation therapy for 2 to 3 years beginning 2 months before radiation therapy
  - Note that androgen deprivation therapy improves 10-year survival in this population, with an NNT of 6

- For patients who are undergoing external-beam radiotherapy for nonbulky clinically localized prostate cancer that is high risk only by serum PSA level or Gleason sum (PSA level >20.0 ng/mL, Gleason sum 8 to 10, or both), consider giving androgen deprivation therapy for 6 to 36 months with radiation therapy.

- Consider recommending 6 months of androgen deprivation therapy for men undergoing external-beam radiation with PSA of 10.0 to 20.0 ng/mL or a Gleason sum of 7 who do not meet the high-risk criteria for a longer course of androgen deprivation therapy.

- See table Drug Treatment for Prostate Cancer.
Evidence

- A 2013 guideline from the European Society of Medical Oncology stated that options for patients with intermediate-risk prostate cancer include radical prostatectomy, external-beam radiation with androgen deprivation therapy, or high-dose brachytherapy (39).

- A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended offering radical prostatectomy and radical radiotherapy as options for men with high-risk localized disease, in whom long-term disease control seems likely. For men receiving external-beam radiation, the guideline recommended a conformational approach and the coadministration of hormonal therapy for 2 years in men with Gleason scores ≥8.

- A randomized trial compared radiation therapy alone to radiation therapy plus 4 months of androgen deprivation therapy in 1979 subjects with T1b-T2b prostate cancer and a PSA level of <20.0 ng/mL. After a mean follow-up time of 9 years, prostate cancer mortality was lower in the androgen deprivation group (4% vs. 8%, P=0.001). Overall survival was higher in the androgen deprivation group (62%) than in the radiotherapy-alone group (57%, P=0.03). A stratified analysis found that most of this benefit occurred in intermediate-risk patients (90).

- A European study randomly assigned 875 patients with locally advanced prostate cancer (predominantly T3 lesions) to receive either hormonal therapy or hormonal therapy plus radiation therapy. Hormonal therapy consisted of androgen blockade (e.g., gonadotropin-releasing hormone agonist plus an anti-androgen) for 3 months followed by continuous monotherapy with flutamide, 250 mg orally 3 times a day. The majority of men received breast irradiation for gynecomastia, likely due to the anti-androgen. The cumulative incidence of overall mortality at 10 years was 39.4% in the hormone-only group compared with 29.6% in the combined-treatment group (P<0.004). Urinary, rectal, and sexual problems were slightly more common in patients receiving both hormonal and radiation therapies (91).

- A randomized trial compared radiation therapy alone or radiation therapy plus immediate treatment with 3 years of goserelin (plus cyproterone acetate for the first 4 weeks following the first goserelin injection) in 415 men with locally advanced prostate cancer. The 10-year clinical disease-free survival was 22.7% in patients receiving radiation therapy alone compared with 47.7% in patients receiving combined treatment (P<0.0001). In addition, the 10-year overall survival was 39.8% and 58.1% (NNT=6; P=0.0004), respectively, and the 10-year prostate cancer mortality was 30.4% and 10.3% (NNT=5; P<0.0001), respectively. The addition of ADT was not associated with a significant difference in cardiovascular mortality (104).

- A randomized trial compared surveillance or an additional 24 months of goserelin in 1554 men with locally advanced prostate cancer who were initially treated with external-beam radiation plus 4 months of goserelin plus flutamide (starting 2 months before radiation). After a median follow-up time of 11 years, the goserelin group had better disease-free survival compared to the surveillance group (22.5% vs. 13.2%, P<0.0001) and lower rates of distant metastases (14.8% vs. 22.8%, P<0.0001), but rates of overall survival were similar (53.9% vs. 51.6%, P=0.36) (105).

- A randomized trial compared lifelong androgen deprivation therapy with RT (65 to 69 Gy to the prostate and seminal vesicles, 45 Gy to the pelvic nodes) to androgen deprivation therapy alone in patients with locally advanced (T3 or T4, or T2 with high PSA or Gleason score) prostate cancer. After a median follow-up time of 6 years, mortality was lower in the combination-therapy group (24.0%) than the hormonal therapy-alone group (29.1%). A small effect of RT on late GI toxicity was noted (106; 107).

Rationale

- Androgen deprivation therapy has been shown to prolong overall survival in men with bulky or locally advanced disease.

Comments
• Although there is a consensus that locally advanced prostate cancer should be treated with androgen ablation plus external-beam radiation, several issues remain poorly defined and unresolved, for example, the optimal duration of androgen ablation; the utility of including an NSAA alone or in addition to a GnRH agonist (as opposed to using a GnRH agonist alone), and the extent to which Gleason sum and serum PSA level should influence decisions about the duration of androgen ablation. The trials discussed most clearly show a benefit for men with one or more of the following features: bulky tumors, T3 or T4 disease, or pelvic lymph-node metastases.

• The reason ADT improves outcomes is unclear, but it may accentuate the cytotoxicity of external-beam radiation; in addition, it may eradicate micrometastatic disease and therefore decrease the risk for systemic failure.

• Although one of the trials discussed used orchiectomy for androgen ablation, it would not be considered a standard option today because it results in permanent androgen ablation, which is associated with substantial side effects. It is unclear whether permanent ablation offers a benefit over temporary ablation.

6.8 **Discuss the potential adverse effects of androgen deprivation therapy with patients who are considering it.**

**Recommendations**

• Discuss with patients the potential adverse effects of androgen deprivation therapy, including loss of libido, hot flashes, fatigue, gynecomastia, loss of muscle mass, osteoporosis, and depression.

• Advise patients of the possible association between gonadotropin-releasing hormone agonists and increased risk for diabetes and cardiovascular disease, and consider screening and following modifiable cardiovascular markers, such as increased serum glucose levels, risk of osteoporosis, and hypertension.

• In patients who choose to undergo androgen deprivation therapy:
  • Evaluate for the use of a bisphosphonate in men at high risk for fracture
  • Recommend regular exercise
  • Consider interventions to manage symptoms associated with ADT

**Evidence**

• A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended that men receiving androgen deprivation therapy be advised to exercise.

• A 2011 systematic review of treatments for localized prostate cancer for the U.S. Preventive Services Task Force included two randomized trials and nine cohort studies evaluating benefits and two randomized trials, 14 cohort studies, and 11 other studies evaluating harms. There was benefit to prostatectomy compared with watchful waiting in one randomized trial and eight cohort studies, with an NNT of 15 for all-cause mortality after 15 years in the randomized trial and a hazard ratio for all-cause mortality in observational data ranging from 0.41 to 0.50. Cohort studies showed mortality benefit to radiation therapy compared with watchful waiting (median adjusted HR, 0.68 [CI, 0.62 to 0.81]). Harms were estimated mostly from cohort studies; there was an additional patient with erectile dysfunction for every three men treated with prostatectomy, seven men treated with radiation therapy, or two to three men treated with androgen deprivation therapy, and one additional patient with urinary incontinence for every five men treated with prostatectomy (74).

• A 2011 systematic review of rates of cardiac death with androgen deprivation therapy in men with prostate cancer included eight randomized trials with 4141 participants. Androgen deprivation therapy did not increase cardiovascular mortality (RR, 0.93 [CI, 0.79 to 1.10]) but did improve prostate cancer survival with RR, 0.69 (CI, 0.56 to 0.84) and all-cause mortality RR, 0.86 (CI, 0.80 to 0.93) (108).
• A 2006 Cochrane review of bisphosphonates for pain in advanced prostate cancer included 10 studies with 1955 participants. There was a trend toward better pain relief with bisphosphonates compared with placebo (response rates 27.9% vs. 21.1%, \( P=0.07 \)). Skeletal event rates in the bisphosphonate group (37.8%) were lower than in the placebo group (43.0%) (OR, 0.79 [CI, 0.62 to 1.00]) (109).

• A 2006 systematic review of bisphosphonates in men with advanced prostate cancer included 10 trials assessing clodronate, alendronate, pamidronate, etidronate, and zoledronic acid. Only three trials reported outcomes for skeletal events. One study of zoledronic acid found fewer skeletal events in the zoledronic acid group, but there was no difference in quality of life and there were adverse effects of the medication (110).

• A randomized trial compared denosumab, a fully human monoclonal antibody against the receptor activator of nuclear factor-\( \kappa \)B ligand, or RANKL, to placebo in 1468 men treated with androgen deprivation therapy for nonmetastatic prostate cancer. The primary outcome was bone mineral density, but fracture rates were reported as secondary outcomes. After 36 months, rates of vertebral fracture were lower in the denosumab group (1.5% vs. 3.9% with placebo; NNT=42) but no difference in rates of overall fractures. Bone density was higher in the denosumab group (111).

• A small prospective cohort study evaluated the effect of ADT on physical function (endurance, grip strength, and lower body strength) and quality of life (SF-36 Health Survey scores) Men with nonmetastatic prostate cancer who were starting ADT were matched with two similarly aged groups of men (men with prostate cancer who were not taking ADT and healthy controls), with assessments at baseline and 3, 6, and 12 months. Among men taking ADT, endurance, grip strength, and physical components of the SF-36 Health Survey were affected within 3 months of starting ADT (112).

• A randomized trial compared resistance and aerobic exercise to usual care in 57 men with prostate cancer who were receiving androgen deprivation therapy. After 12 weeks, the exercise group had better muscle strength, greater lean body mass, less fatigue, and better self-rated overall health than the usual-care group (113).

• A randomized trial compared the efficacy of venlafaxine, 75 mg/d; medroxyprogesterone acetate, 20 mg/d; or cyproterone acetate, 100 mg/d, in 309 men with prostate cancer who experienced hot flashes during treatment with androgen deprivation therapy. After 6 months, all three medications proved to be effective in reducing hot flashes, with cyproterone and medroxyprogesterone more effective than venlafaxine. The authors point out that cyproterone treatment could interfere with hormonal therapy (114).

• A large cohort study evaluated outcomes after androgen deprivation therapy in 37,443 men treated in the Veterans Affairs health system. GnRH agonist use was associated with an increased risk for diabetes (adjusted HR, 1.28) and coronary heart disease (adjusted HR, 1.19) as well as myocardial infarction (adjusted HR, 1.28), sudden cardiac death (adjusted HR, 1.35), and stroke (adjusted HR, 1.22) (115).

**Rationale**

• The adverse effects of androgen deprivation therapy are well established and include a range of metabolic toxicities and side effects that negatively affect quality of life.

• Consideration of these adverse effects is critical when selecting patients for ADT and when counseling patients about androgen deprivation therapy.

**Comments**

• None.

**6.9 Recommend androgen deprivation therapy (hormone therapy) for patients with metastatic prostate cancer.**
Recommendations

- Recommend ADT for patients with metastatic prostate cancer involving bone, liver, lung, or any lymph nodes, using one of the following approaches:
  - Gonadotropin-releasing hormone agonist, such as leuprolide or goserelin, with or without a nonsteroidal anti-androgen, such as bicalutamide or flutamide
  - Gonadotropin-releasing hormone antagonist, such as degarelix
  - Bilateral subcapsular orchiectomy

- When starting a GnRH agonist:
  - Do not start therapy in patients with prostate cancer-related pain, epidural disease, symptoms of urinary obstruction, or spinal cord compression until androgen receptor blockade has been achieved medically via NSAA
  - Consider starting a 4-week course of an NSAA 1 to 2 weeks beforehand in order to inhibit cancer growth during the brief surge in serum testosterone that follows the initial GnRH agonist injection
  - Alternatively, consider orchiectomy or a GnRH antagonist in patients at risk for flare symptoms, because these therapies do not result in an initial surge in testosterone levels.

- In patients with metastatic disease who progress while on pharmacologic androgen deprivation therapy, recommend bilateral orchiectomy if serum testosterone is not at castrate levels (i.e., <50 ng/dl).

- Discuss possible intermittent androgen deprivation versus continuous androgen deprivation in patients with metastatic hormone-sensitive prostate cancer.

- See table Drug Treatment for Prostate Cancer.

Evidence

- A 2013 guideline from the European Society of Medical Oncology on the management of prostate cancer recommended that patients with metastatic disease be treated with androgen suppression using bilateral orchiectomy or an LHRH agonist/antagonist (39).

- A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended that men with metastatic disease receive either androgen deprivation therapy using medication or with bilateral orchiectomy.

- A 2011 systematic review of rates of cardiac death with androgen deprivation therapy in men with prostate cancer included eight randomized trials with 4141 participants. Androgen deprivation therapy did not increase cardiovascular mortality (RR, 0.93 [CI, 0.79 to 1.10]) but did improve prostate cancer survival with RR, 0.69 (CI, 0.56 to 0.84) and all-cause mortality RR, 0.86 (CI, 0.80 to 0.93) (108).

- A 2011 systematic review of treatments for localized prostate cancer for the U.S. Preventive Services Task Force included two randomized trials and nine cohort studies evaluating benefits and two randomized trials, 14 cohort studies, and 11 other studies evaluating harms. There was benefit to prostatectomy compared with watchful waiting in one randomized trial and eight cohort studies, with an NNT of 15 for all-cause mortality after 15 years in the randomized trial and a hazard ratio for all-cause mortality in observational data ranging from 0.41 to 0.50. Cohort studies showed mortality benefit to radiation therapy compared with watchful waiting (median adjusted HR, 0.68 [CI, 0.62 to 0.81]). Harms were estimated mostly from cohort studies; there was an additional patient with erectile dysfunction for every three men treated with prostatectomy, seven men treated with radiation therapy, or two to three men treated with androgen deprivation therapy, and one additional patient with urinary incontinence for every five men treated with prostatectomy (74).

- A randomized trial compared immediate androgen deprivation therapy to delayed therapy (at the time of recurrence or distant metastases) in 98 men with node-positive prostate cancer who had
undergone radical prostatectomy. After a median follow-up time of 12 years, overall mortality (36% vs. 55%, P=0.04) and prostate-cancer mortality (15% vs. 49%, P=0.0004) were lower in the immediate-therapy group than in the delayed-therapy group (101).

- A randomized non-inferiority trial compared intermittent and continuous androgen deprivation therapy in 1386 patients with elevated PSA (>3 ng/mL) after radiotherapy for localized prostate cancer. After a median follow-up time of 6.9 years, overall mortality was similar in the intermittent-therapy (38.8%) and continuous-therapy (36.8%) groups (HR, 1.02 [CI, 0.86 to 1.21]), which met criteria for non-inferiority (102).

- A randomized non-inferiority trial compared continuous androgen deprivation to intermittent androgen deprivation in 1739 men with metastatic prostate cancer and initial PSA ≥ 5 ng/mL in whom PSA was reduced to <4 ng/mL with 7 months of initial androgen deprivation therapy. After a median follow-up time of 9.8 years, the analysis included 1535 men. There was a trend toward a higher rate of death in the intermittent-therapy group (HR, 1.10 [CI, 0.99 to 1.23]); intermittent therapy was determined not to be non-inferior to continuous therapy (116).

Rationale

- Androgen deprivation therapy is the most highly active systemic therapy for prostate cancer and probably increases survival for men with newly diagnosed metastatic prostate cancer.

- GnRH agonists result in a reduction in serum testosterone levels comparable to surgical castration (orchiectomy).

Comments

- GnRH agonists are currently the most popular method to achieve castration.

- Orchiectomy remains an appropriate alternative. Men may be concerned about cosmetic issues, but GnRH agonists result in marked testicular atrophy, which may also have cosmetic consequences.

- Diethylstilbestrol has cardiovascular toxicity and is not commonly used at this time as primary therapy, but DES continues to have a potential role in the secondary hormonal setting.

- Degarelix is a GnRH antagonist approved by the FDA in 2008 for the treatment of advanced prostate cancer. Degarelix lowers testosterone much more quickly than GnRH agonists. Although this may be of particular benefit in patients with critical sites of metastatic disease (e.g., spinal cord compression), the importance of the rapid reduction in testosterone is less clear for the majority of patients with advanced prostate cancer but without a site of critical metastasis (117).

6.10 Consider palliative external-beam radiation therapy for men with castration-resistant prostate cancer and painful bone metastases.

Recommendations

- Consider recommending external-beam radiation therapy to painful bone metastases in patients with castration-resistant prostate cancer.

Evidence

- A 2013 guideline from the European Society of Medical Oncology recommended offering radiation therapy for men with painful bone metastases for whom hormonal therapy was ineffective (39).

- A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended considering strontium-89 for men with painful bone metastases from hormone-refractory prostate cancer.

- A 2004 Cochrane review of radiation therapy for palliation of painful bone metastases included 11 trials with 3435 participants, among whom 24% had prostate cancer. Overall, single-fraction and multifraction radiation resulted in similar levels of pain relief; rates of pain response were 34% for single-fraction radiation and 32% for multifraction (118).
Rationale

- External-beam radiation therapy is a well-tolerated, safe, and proven method to relieve bone pain associated with metastases from prostate cancer, particularly in patients with localized pain from a metastatic bone lesion.
- External-beam radiation therapy also has a role in the management of unstable bone lesions in the spine, pelvis, and legs that have already fractured or are at risk for fracture.

6.11 Administer chemotherapy in patients with metastatic castration-resistant prostate cancer that is symptomatic or rapidly progressing, generally with docetaxel as first-line therapy.

Recommendations

- Administer chemotherapy for patients with metastatic castration-resistant prostate cancer whose disease is progressing despite medical or surgical castration.
- Consider docetaxel, 75 mg/m² of body surface every 21 days, with prednisone, 5 mg twice daily, in patients with metastatic castration-resistant prostate cancer, particularly if symptomatic or rapidly progressing.
- Consider mitoxantrone, 12 mg/m² intravenous bolus every 21 days, plus either hydrocortisone, 20 mg every morning and 10 mg every night, or prednisone, 10 mg/d orally, in patients who exhibit progressive disease on or after docetaxel or who are fit for docetaxel chemotherapy.
- Consider cabazitaxel, 25 mg/m² intravenously every 21 days, plus prednisone, 10 mg/d orally, in select patients who exhibit progressive disease during or after docetaxel administration.
- If considering cabazitaxel, assess the appropriateness of using myeloid growth factors in all patients, especially the elderly, as cabazitaxel is associated with significant myelosuppression and diarrhea.
- If using mitoxantrone chemotherapy, check left ventricular function before beginning treatment, after a cumulative dose of about 100 mg/m², and after every two to three subsequent doses.
- See table Drug Treatment for Prostate Cancer.

Evidence

- A 2013 guideline from the European Society of Medical Oncology recommended that men with progressive metastatic disease despite hormonal therapy be offered either chemotherapy or secondary hormonal therapy, noting that docetaxel is the first-line chemotherapeutic agent and that cabazitaxel is effective in patients who have failed docetaxel (39).
- A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended docetaxel for men with hormone-refractory prostate cancer and good performance status.
- A 2006 Cochrane review of chemotherapy for hormone-refractory prostate cancer included 47 trials with 6929 participants. Results were not pooled due to variable comparisons. Only studies of docetaxel showed improved survival compared with usual care, though the improvement was <2.5 months. Mean rates of PSA response were 52% with docetaxel, 48% with estramustine, 50% with doxorubicin, 33% with mitoxantrone, and 20% with 5-fluorouracil (119).
- A 2006 systematic review of therapies for hormone-refractory metastatic prostate cancer included 27 randomized trials. Results were not pooled, but two large trials found improved survival with docetaxel compared with mitoxantrone plus prednisone and better quality of life (120).

Rationale

- Chemotherapy using docetaxel has been shown to improve overall survival in men with metastatic castration-resistant disease relative to other agents.
• Chemotherapy has been shown to result in an improved quality of life in men with symptomatic castration-resistant disease.

• Chemotherapy with cabazitaxel after docetaxel chemotherapy has been shown to improve overall survival but is associated with substantial side effects, including bone-marrow suppression, neutropenic fevers, and diarrhea.

• Mitoxantrone was the first approved cytotoxic chemotherapy for prostate cancer and is associated with a palliative effect. It can also cause life-threatening cardiomyopathy, which requires appropriate patient selection and monitoring.

Comments
• In June 2010, the FDA approved cabazitaxel for use in combination with prednisone for treatment of patients with metastatic castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy. The approval includes a recommendation to consider use of granulocyte colony-stimulating factor to reduce the risk for neutropenic complications in patients with high-risk features, including being over the age of 65, poor performance status, extensive previous radiation therapy, and previous febrile neutropenia. Premedication with an antihistamine, a corticosteroid, and an H2-receptor blocker also is recommended to prevent severe hypersensitivity reaction.

6.12 Consider administering a corticosteroid to patients with symptomatic, metastatic, progressive, castration-resistant prostate cancer.

Recommendations
• In patients with symptomatic, metastatic, progressive, castration-resistant prostate cancer, consider one of the following:
  • Prednisone, 10 mg/d orally
  • Dexamethasone, 0.5 to 2 mg/d orally
  • Hydrocortisone, 30 mg orally every morning and 10 mg orally every night
• See table Drug Treatment for Prostate Cancer.

Evidence
• A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended a corticosteroid as a third-line agent for patients with hormone-refractory prostate cancer.

• A trial compared hydrocortisone with hydrocortisone plus mitoxantrone in men with hormone-refractory prostate cancer. Among the 123 patients who received hydrocortisone alone, 8% reported a significant reduction in pain, and 22% experienced a greater than 50% decrease in serum PSA. Pain control and PSA response were superior, however, among the patients who also received mitoxantrone (121).

• A randomized phase-III trial compared prednisone with prednisone plus mitoxantrone in men with hormone-refractory prostate cancer. Among 81 patients receiving prednisone alone, 12% reported a significant reduction in pain and 18% experienced a greater than 50% reduction in serum PSA levels. Pain control and PSA response were superior, however, among the patients who also received mitoxantrone (122).

• A small study of low-dose dexamethasone reported that 11 of 18 patients (61%) reported a significant decrease in pain and 23 of 37 patients (62%) had a greater than 50% decline in serum PSA (123).

Rationale
• Corticosteroids have been shown to reduce PSA levels and provide palliation to patients with castration-resistant prostate cancer.

Comments
• Corticosteroids are commonly used in patients with advanced prostate cancer. They specifically are given to patients receiving docetaxel, mitoxantrone, cabazitaxel, or abiraterone. The role of corticosteroid monotherapy in advanced prostate cancer has yet to be determined, as many patients are receiving corticosteroids via the combinations noted.

6.13 Consider using diethylstilbestrol or a nonsteroidal anti-androgen for patients with advanced localized or metastatic prostate cancer that progresses despite treatment with androgen deprivation therapy.

Recommendations
• In patients with a rising serum PSA level or radiographically progressive disease despite medical or surgical castration, consider starting DES or a nonsteroidal anti-androgen:
  • Bicalutamide, 50 mg/d
  • DES, 1 mg up to three times daily
  • High-dose bicalutamide, 150 mg/d
  • Standard-dose flutamide, 250 mg orally three times daily
• In patients whose PSA level rises or who have radiographically progressive disease while using a nonsteroidal anti-androgen, discontinue the nonsteroidal anti-androgen but continue the gonadotropin-releasing hormone agonist indefinitely on those already receiving one.
• Do not generally use dual anti-androgen therapy as a first-line therapy.
• See table Drug Treatment for Prostate Cancer.

Evidence
• A 2013 guideline from the European Society of Medical Oncology on the management of prostate cancer recommended that patients with metastatic disease be treated with androgen suppression using bilateral orchiectomy or an LHRH agonist/antagonist and stated that combination anti-androgen therapy can be considered for men who progress despite first-line hormonal therapy (39).
• A 2002 systematic review of combined androgen deprivation therapy compared to monotherapy in men with advanced prostate cancer included 21 trials. At 2 years, there was no survival difference between the combined and monotherapy groups (HR, 0.97 [CI, 0.87 to 1.1]) but at 5 years the combined group had a lower rate of mortality (HR, 0.87 [CI, 0.81 to 0.94]). More patients on combined therapy withdrew due to side effects (124).
• A randomized trial compared DES, 1 mg three times daily, plus aspirin, 75 mg daily, or to flutamide, 250 mg three times daily in 28 men with relapsed prostate cancer after hormonal therapy. Men receiving DES experienced a significantly greater average decrease in serum PSA than men receiving flutamide (65% decline vs. 35% decline; P=0.034). Median survival was 18 months in the DES arm compared with 11 months in the flutamide arm, but this difference was not statistically significant (P=0.31) (125).

Rationale
• Men who have been medically or surgically castrated have low levels of circulating testosterone that may stimulate growth of prostate cancer.
• Nonsteroidal anti-androgens block the androgen receptor and thus may have an additive effect over androgen deprivation therapy alone, since some residual testosterone persists despite androgen deprivation therapy.
• Men who have been treated with a nonsteroidal anti-androgen may undergo mutation or up-regulation of the androgen receptor on cancer cells such that the nonsteroidal anti-androgen has an agonist rather antagonist effect on the receptor.
Comments

- Diethylstilbestrol was replaced by GnRH agonists as the primary medical therapy in the 1980s because of the cardiovascular toxicity associated with estrogens. As a result, DES is not commonly used at this time as primary therapy, but DES continues to have a potential role in the secondary hormonal setting.

- Due to cardiovascular and thromboembolic toxicity seen in older trials using higher doses, most clinicians administering DES do so at a lower dose (e.g., 1 mg/d). DES is currently only available in the U.S. through specialty and compounding pharmacies, significantly limiting its widespread use.

6.14 Consider the use of a CYP17 inhibitor or an inhibitor in the androgen receptor signaling pathway in patients with advanced prostate cancer.

Recommendations

- Consider prescribing a CYP17-inhibiting agent, such as abiraterone acetate, for patients with metastatic, castration-resistant prostate cancer with progressive disease. A decision to start a CYP17 inhibitor is generally made in consultation with a medical oncologist.

- If prescribing abiraterone acetate, give the recommended dose of 1000 mg orally once daily in combination with prednisone, 5 mg orally twice daily. Note that symptoms related to excess mineralocorticoid, including hypokalemia, hypertension, and peripheral edema, have been observed with abiraterone.

- Monitor patients on abiraterone acetate for evidence of hepatocellular toxicity by measuring serum liver function every 2 weeks initially and then periodically.

- Consider prescribing an inhibitor of the androgen receptor signaling pathway, such as enzalutamide, for patients with metastatic, castrate-resistant prostate cancer after chemotherapy failure.

- See table Drug Treatment for Prostate Cancer.

Evidence

- A phase-III randomized trial of 1195 patients with disease progression after docetaxel-based chemotherapy compared treatment with 5 mg of prednisone twice daily plus either 1000 mg/d of abiraterone acetate (n=797) or placebo (n=398). The primary end point was overall survival. The study was stopped early after median follow-up of 12.8 months. The abiraterone group had lower mortality (42% vs. 55%; NNT=10), and statistically significant improvements were seen with abiraterone acetate in all secondary end points (time to PSA progression, progression-free survival, and PSA response). Abiraterone acetate was associated with significantly higher rates of mineralocorticoid-related adverse events, including fluid retention, edema, hypokalemia, and hypertension (126).

- A randomized trial compared abiraterone acetate (1000 mg) plus prednisone (5 mg twice daily) or placebo plus prednisone in 1088 patients with metastatic castration-resistant prostate cancer. After a planned unblinding of the study, the median follow-up time was 22 months. Mortality was lower in the combination-therapy group (27%) than in the prednisone-alone group (34%), with HR, 0.75 (CI, 0.61 to 0.93), but this did not reach predetermined levels of statistical significance (127).

- A phase-III randomized trial compared oral enzalutamide at a dose of 160 mg per day (800 patients) or placebo (399 patients) in 1199 men with castration-resistant prostate cancer after chemotherapy. The study was stopped after a planned interim analysis at the time of 520 deaths. The median overall survival was 18.4 months (CI, 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (CI, 11.3 to 15.8) in the placebo group (HR for death in the enzalutamide group, 0.63 [CI, 0.53 to 0.75]; P<0.001) (128).

Rationale
• Androgen receptor signaling plays a major role in the pathogenesis of prostate cancer and is an important treatment target even in patients previously classified as having androgen-independent disease. CYP17 is a key enzyme for androgen biosynthesis in both the testes and adrenal gland and is highly expressed in tumor tissue. Ketoconazole weakly and nonspecifically inhibits CYP17; abiraterone acetate selectively and potently inhibits CYP17.

Comments
• In April 2011, the FDA approved abiraterone acetate, 1000 mg orally once daily, in combination with prednisone, 5 mg orally twice daily, for use in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy.
• There is no evidence that ketoconazole prolongs survival, and with the advent of new treatment options, use of ketoconazole is declining.

6.15 Consider autologous cellular immunotherapy for patients with metastatic castration-resistant prostate cancer and no or minimal symptoms.

Recommendations
• Consider autologous cellular immunotherapy with sipuleucel-T, given 2 weeks for 3 treatments, for patients with metastatic castration-resistant prostate cancer and no or minimal symptoms.
• Explain to patients that autologous cellular immunotherapy uses cells from the patient’s own immune system and that they will need to undergo a cell collection process (leukapheresis) before each treatment.
• Advise patients of the most common side effects of autologous cellular immunotherapy, pyrexia and rigor, which are generally limited to the peri-infusional period.
• See table Drug Treatment for Prostate Cancer.

Evidence
• A phase-III randomized trial compared sipuleucel-T \( (n=82) \) or placebo \( (n=45) \) in patients with asymptomatic metastatic castration-resistant prostate cancer. Infusions of study drug were given every 2 weeks for a total of three infusions. The primary end point was time to disease progression; overall survival was assessed secondarily. Complete follow-up to 36 months was obtained in all surviving subjects. There was a trend toward longer time to disease progression in the sipuleucel group (HR, 1.45; CI, 0.99 to 2.11). Survival at 36 months was higher in the sipuleucel group (34% vs. 11%; NNT=4; \( P=0.005 \)) (129).

• A randomized trial compared sipuleucel-T \( (n=341) \) or placebo \( (n=171) \) in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. Study drug was given every 2 weeks for a total of three infusions. The primary end point was overall survival. After median follow-up of 34.1 months, mortality rates were 61.6% in the sipuleucel-T group and 70.8% in the placebo group (NNT=12; \( P=0.03 \)). Common adverse effects of sipuleucel-T were chills (51.2%), fever (22.5%), fatigue (16.0%), nausea (14.2%), and headache (10.7%); most were mild or moderate in severity (130).

Rationale
• The treatment is personalized for each patient. The patient undergoes leukapheresis to enrich for selection of antigen-presenting cells, which are then sent to a central processing facility and cultured with PA2024, a fusion protein containing a prostate antigen and a stimulatory entity. The cells are then reinfused as autologous cellular immunotherapy. PA2024 consists of a prostate antigen, a prostatic acid phosphatase, an immune stimulator, and a granulocyte-macrophage colony-stimulating factor. The treatment is designed to stimulate T-cell immunity against prostatic acid phosphatase.
Comments

- In April 2010, the FDA approved sipuleucel-T for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. Sipuleucel-T is an autologous cellular immunotherapy (therapeutic vaccine) that is administered intravenously in a three-dose schedule given at 2-week intervals.
7. Patient Counseling

Recognize the importance of involving patients with prostate cancer early in the course of their disease.

7.1 Encourage patients with prostate cancer to assume a primary role in their care, including issues related to choice of treatment and ongoing care.

Recommendations

- Discuss with patients:
  - The accuracy and limitations of PSA testing at predicting or excluding a diagnosis of prostate cancer
  - Imaging and biopsy modalities
  - Definitive surgical options, including nerve-sparing techniques
  - Recovery from surgery, including the need to have a Foley catheter for several weeks after surgery and the likelihood of temporary postoperative incontinence when the catheter is removed
  - The risk for impotence after surgery or radiation therapy and the available remedies should impotence occur
  - The potential side effects of radiation therapy and the importance of avoiding sun exposure and using skin moisturizers to minimize toxicity effects
  - Indications for and potential side effects of hormonal and chemotherapeutic agents (see information on side effects of systemic hormonal therapy and chemotherapy)
  - Psychosocial issues, including family dynamics and available support systems

Evidence

- Consensus.

Rationale

- Evaluation and treatment of prostate cancer is complex and involves ongoing decision-making.
- Side effects of treatment can have a significant effect on men’s quality of life and self-esteem.

7.2 Inform patients of potential benefits and short- and long-term side effects of systemic hormonal therapy and chemotherapy.

Recommendations

- Recommend an effective antinausea regimen for patients on chemotherapy.
- Remind patients of the importance of seeking early medical care with fevers or severe diarrhea while on chemotherapy.
- Make patients aware of potential long-term effects of medical therapy, including risk for:
  - Permanent hypogonadism after even short-term use of gonadotropin-releasing hormone agonists and associated risks for:
    - Loss of libido
    - Osteoporosis
    - Hot flashes
    - Depression
    - Loss of muscle mass
    - Gynecomastia
    - Fatigue
    - Weight gain
    - Metabolic syndrome
• Erectile dysfunction
  • Late-onset ventricular dysfunction following chemotherapy with mitoxantrone
  • Peripheral neuropathy following chemotherapy with docetaxel
  • Infection and likelihood of hair loss, hypersensitive reactions, diarrhea, nausea, and fatigue with chemotherapy
  • Potential for hypertension, edema, and hypokalemia with CYP17 inhibitors, such as abiraterone acetate
  • Liver toxicity with abiraterone acetate and nonsteroidal anti-androgens and the need to have liver function monitored
  • Peri-infusional reactions, including fever and rigor, with autologous cellular immunotherapy
• In patients with metastatic disease, discuss the choice of treatments that involve tradeoffs between toxicity and palliation of symptoms.

Evidence
• Consensus.

Rationale
• Decisions about adjuvant treatment often involve personal decisions weighing treatment morbidity with the potential risk for recurrence.

7.3 Discuss with patients the plan for ongoing follow-up after completion of initial therapy.

Recommendations
• Inform patients about the need to monitor for evidence of relapse and response to treatment by measuring serum PSA levels periodically:
  • Measure serum PSA level every 3 to 12 months after radical prostatectomy or radiation therapy for the first 5 years and annually thereafter
  • Measure serum PSA levels every 1 to 3 months during androgen deprivation therapy and chemotherapy
• Stress the importance of periodic visits to members of a multidisciplinary team:
  • Alternate routine visits with members of the cancer care team every 3 to 6 months for the first 2 to 3 years after primary therapy, then every 6 to 12 months for the next 2 years, and then annually
  • For patients having surgery or radiation, continue alternative exclusive follow-up with their surgeon or radiation oncologist
  • After the first 5 years of follow-up, consider discontinuing regular visits with cancer specialists and continue follow-up with a primary care provider with an interest in men's health issues
• Encourage patients to make sure their cancer doctors coordinate cancer care with the patient's primary care providers to avoid duplication of efforts.
• Inform patients that no imaging studies or additional blood tests other than serum PSA are needed to monitor for relapse or progression unless there are signs or symptoms of progressive disease or relapse.

Evidence
• A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended that men who undergo aggressive treatment for prostate cancer have a PSA level checked 6 weeks after the start of treatment, then every 6 months for 2 years, then annually.
  • Mainly consensus.

Rationale
• Serum PSA is the most sensitive test for progression and regression of prostate cancer, although some prostate cancers (typically high-grade tumors) do not release significant amounts of PSA.

Comments
• The patient's PSA levels may have a variable course in the first year or more after radiation therapy before eventually becoming unmeasurable, making the interpretation of postradiation PSA values challenging.

• The NCCN has issued guidelines for the management of prostate cancer, which are available for clinical use on their web site.
8. Follow-up  

Follow patients with prostate cancer indefinitely for recurrence of disease. 

8.1 Monitor patients at least annually to survey for recurrent disease after definitive local therapy with radical prostatectomy, radiation therapy, or seed implants. 

Recommendations

- Measure the serum PSA level every 3 to 12 months for the first 5 years after primary therapy, depending on the patient's risk factors.
- Spread out PSA surveillance annually after 5 years if the patient shows no evidence of relapse.
- Include in surveillance a measurement of serum PSA and an interval history and examination to evaluate for signs or symptoms of relapse.
- **High-value care:** Do not check PSA in asymptomatic men who are poor candidates for aggressive therapy.
- **High-value care:** Do not routinely obtain imaging studies, such as a bone or CT scan, unless specifically indicated by signs or symptoms or recurrence.

Evidence

- A 2014 NICE (UK) guideline on the diagnosis and treatment of prostate cancer recommended that men who undergo aggressive treatment for prostate cancer have a PSA level checked 6 weeks after the start of treatment, then every 6 months for 2 years, then annually.
- Three large case series involving a total of about 2000 men who had undergone radical prostatectomy and were being followed with periodic serum PSA determinations and digital rectal examinations reported that no men were found to have a local recurrence via DRE before having an elevation in serum PSA (131; 132; 133).

Rationale

- Although most men having prostatectomy or radiation therapy are apparently cured by those treatments, a significant number of patients relapse, and the risk for relapse varies with the specific attributes of an individual's disease.
- Serum PSA level is the most sensitive and specific test for detecting relapse, although postradiation PSA “bounces” can occur and may not be indicative of recurrence.

Comments

- A rising PSA level after radical prostatectomy or radiation therapy indicates relapsed prostate cancer, but most men (66% in one large series [134]) with a biochemical relapse do not go on to develop radiologically detectable metastases or die of prostate cancer.
- The NCCN has issued guidelines for the management of prostate cancer, which are available for clinical use on their web site.

8.2 Monitor men with advanced prostate cancer every 1 to 3 months and test and treat as needed. 

Recommendations

- Evaluate men with advanced disease every 1 to 3 months with a history, examination, and PSA determination.
• In men with progressive pain or other symptoms, order bone scans and other imaging studies as needed.

• In men with new or worsening back pain, obtain an emergent MRI of the spine to look for spinal cord compression.

• Refer patients with painful metastases for radiation therapy, medical therapy, or both.

• Consider making appropriate changes in hormonal therapy or initiating chemotherapy in conjunction with the consulting medical oncologist.

• Consider referring patients with pain to a pain or palliative care specialist.

Evidence
- Consensus.

Rationale
- Advanced disease tends to progress over time, leading to pain, bone fractures, spinal cord compression, declining functional status, and other complications.

- Preventing or responding promptly to such problems can improve quality of life.
References


Glossary

5-ARI
5-a-reductase inhibitor

ADT
androgen deprivation therapy

ASCO
American Society of Clinical Oncology

ASTRO
American Society for Therapeutic Radiology and Oncology

AUA
American Urological Association

bid
twice daily

BPH
benign prostatic hyperplasia

CAB
combined androgen blockade

CBC
complete blood count

CI
confidence interval

CKD
chronic kidney disease

CNS
central nervous system

CrCl
creatinine clearance

CT
computed tomography

CV
cardiovascular

CYP
cytochrome P450 isoenzyme

DES
diethylstilbestrol

DRE
digital rectal examination

EBRT
external beam radiotherapy

EPIC
Expanded Prostate Cancer Index Composite

FDA
Food and Drug Administration

GI
gastrointestinal
GnRH
gonadotropin-releasing hormone

G6PD
glucose-6-phosphate dehydrogenase

Gy
gray (unit of absorbed radiation dose)

HR
hazard ratio

im
intramuscular

IMRT
intensity-modulated radiation therapy

iv
intravenous

LVEF
left ventricular ejection fraction

MRI
magnetic resonance imaging

NNT
number needed to treat

NSAA
nonsteroidal anti-androgen

ODAC
Oncologic Drugs Advisory Committee

OR
odds ratio

PAP
prostatic acid phosphatase

P-gp
P-glycoprotein

po
oral

PPV
positive predictive value

PSA
prostate-specific antigen

QALE
quality-adjusted life expectancy

qd
every day

qid
four times daily

RANKL
receptor activator of nuclear factor κB ligand

RR
relative risk

RT
radiation therapy
sc
subcutaneous
SD
standard deviation
SEER
Surveillance, Epidemiology, and End Results
SF-36
Medical Outcomes Study 36-Item Short-Form Health Survey
tid
three times daily
TNM
tumor, node, metastasis
TRUS
transrectal ultrasound of the prostate
TURP
transurethral resection of the prostate
USPSTF
U.S. Preventive Services Task Force
UTI
urinary tract infection

Trials
CaPSURE
Cancer of the Prostate Strategic Urologic Research Endeavor
EORTC 22863
European Organisation for Research and Treatment of Cancer 22863
ERSPC
European Randomised Screening for Prostate Cancer
IMPACT
Immunotherapy for Prostate Adenocarcinoma Treatment
PCPT
Prostate Cancer Prevention Trial
PIVOT
Prostate Cancer Intervention Versus Observation Trial
PLCO
Prostate, Lung, Colorectal, Ovarian
PROSTQA
Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment
REDUCE
Reduction by Dutasteride of Prostate Cancer Events
SEER
Surveillance, Epidemiology, and End Results
SELECT
Selenium and Vitamin E Cancer Prevention Trial
SWOG S9921
Southwest Oncology Group S9921

Terms

**Active surveillance**
Periodic clinical monitoring with curative intervention triggered by signs of disease progression

**CYP17**
cytochrome P-45017 alpha gene

**PSA velocity**
Rate of change in prostate-specific antigen level over time

**Watchful waiting**
Observation and physical examination with treatment of symptoms
### Tables

#### Laboratory and Other Studies for Prostate Cancer

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate-specific antigen</td>
<td>78-100</td>
<td>6-66</td>
<td>BPH, prostatitis, UTI, prostatic stones, manipulation of the prostate or lower urinary tract, and ejaculation can raise PSA. The specificity of PSA is lower in older men. PSA level &gt;50 ng/mL is highly predictive of prostate cancer.</td>
</tr>
<tr>
<td>Prostatic acid phosphatase</td>
<td></td>
<td></td>
<td>Immunohistochemical staining for PAP can help confirm the prostatic origin of metastatic cancers.</td>
</tr>
<tr>
<td>Transrectal ultrasonography</td>
<td>62-78</td>
<td>Unclear</td>
<td>Used to guide biopsy, not for screening or diagnosis. Cancers that are visualized on TRUS typically appear as hypoechoic regions but can also be hyperechoic.</td>
</tr>
<tr>
<td>Prostate biopsy</td>
<td>85-95</td>
<td>100</td>
<td>Lower sensitivity for fewer (six) samples; higher sensitivity with 10 to 12 cores.</td>
</tr>
<tr>
<td>CBC</td>
<td></td>
<td></td>
<td>To detect metastatic prostate cancer in the bone marrow in patients with metastatic disease.</td>
</tr>
<tr>
<td>MRI of the abdomen and pelvis</td>
<td>71 overall</td>
<td></td>
<td>Preferred test for staging in men at risk for advanced disease. Values are for optimizing both sensitivity and specificity.</td>
</tr>
<tr>
<td></td>
<td>64 for extracapsular extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>81 for seminal vesical involvement</td>
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<tr>
<td>CT scan of abdomen and pelvis</td>
<td>55-75 for extracapsular penetration</td>
<td></td>
<td>For staging in men at increased risk for advanced disease.</td>
</tr>
<tr>
<td></td>
<td>32-38 for seminal vesical involvement</td>
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<tr>
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<td>0-100 for lymph-node involvement</td>
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<tr>
<td>Bone scan</td>
<td>92</td>
<td>Poor</td>
<td>Bone is the most common site of metastatic prostate cancer. Specificity is poor; biopsy or additional can help clarify.</td>
</tr>
</tbody>
</table>

BPH = benign prostatic hyperplasia; CBC = complete blood count; CT = computed tomography; MRI = magnetic resonance imaging; NPV = negative predictive value; PAP = prostatic acid phosphatase; PPV = positive predictive value; PSA = prostate-specific antigen; TRUS = transrectal ultrasonography; UTI = urinary tract infection.
## Differential Diagnosis of Prostate Cancer

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>Malignant nodule, sometimes microscopic. Most patients are asymptomatic at presentation.</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>Enlargement of the prostate (usually symmetric), which is common as men age. Characterized by symptoms of urinary outflow obstruction and may cause elevation of serum PSA. Often coexists with prostate cancer. Biopsy distinguishes between the two entities.</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>Inflammatory or infectious state. Dysuria and elevated serum PSA may be present. Bacterial prostatitis is seldom documented in patients suspected of having prostate cancer. Prostatitis is often associated with pelvic pain or tenderness on DRE.</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Osteomyelitis results in increased uptake on bone scans and can be confused with metastatic disease. Osteomyelitis is not associated with an elevated PSA level, and metastatic prostate cancer in the context of a normal PSA level is very unusual. Metastatic prostate cancer tends to be multifocal, whereas osteomyelitis tends to be unifocal. Prostate cancer and osteomyelitis have very different appearances on CT and MRI scans.</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>Bone fractures can result in increased uptake on bone scans and have the appearance of metastases. Plain radiographs should reveal bone fractures, although a CT or MRI scan may be necessary to distinguish pathologic fractures from simple traumatic fractures.</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Degenerative joint disease can result in increased uptake on bone scans and be mistaken for bone metastases by inexperienced radiologists and laypersons. Plain radiographs show joint degeneration and can generally distinguish between osteoarthritis and metastatic prostate cancer. MRI can also be helpful when plain films are inadequate.</td>
</tr>
<tr>
<td>Paget's disease</td>
<td>Paget's disease of the bone can look like sclerotic bone metastases. Paget's disease is not associated with an elevated PSA level, whereas metastatic prostate cancer is. In a patient with known prostate cancer and sclerotic bone lesions, distinguishing Paget's disease from metastases can be difficult.</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td>Sarcoïdosis can result in lymphadenopathy that can mimic metastatic cancer. Sarcoïdosis does not result in an elevated serum PSA. Biopsy specimens of suspicious lesions can definitively distinguish these entities.</td>
</tr>
<tr>
<td>Other cancers</td>
<td>Many other cancers spread to the pelvic and retroperitoneal lymph nodes and the bones, including bladder cancer, colorectal cancer, testicular cancer, renal cell carcinoma, uterine carcinoma, the bladder and the pelvis, and penile cancer. Prostate cancer can generally be distinguished from other malignancies on the basis of histopathologic examination of biopsy specimens.</td>
</tr>
<tr>
<td>Histoplasmosis, blastomycosis, tuberculosis, and coccidiomycosis infection</td>
<td>Indolent fungal and mycobacterial infections can result in lymphadenopathy and visceral nodules that can be mistaken for metastatic disease, but it would be unusual to mistake a fungal infection for prostate cancer. Fungal infections do not result in an elevated PSA. A lymph-node excision is the gold standard for distinguishing neoplastic from infectious causes of adenopathy. These infections are less common than prostate cancer.</td>
</tr>
</tbody>
</table>

BPH = benign prostatic hyperplasia; CT = computed tomography; DRE = digital rectal examination; MRI = magnetic resonance imaging; PSA = prostate-specific antigen.
# Drug Treatment for Prostate Cancer

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Precautions</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gonadotropin-releasing hormone agonists</strong></td>
<td></td>
<td>Hot flashes, testicular atrophy, urinary disorders, CNS and GI side effects, edema, hyperglycemia, bone loss, injection site reactions</td>
<td>Caution with: CV disease, diabetes</td>
<td>Metastatic prostate cancer</td>
</tr>
<tr>
<td>Leuprolide (Lupron Depot)</td>
<td>IM depot options: 7.5 mg IM every month, 22.5 mg IM every 3 months, 30 mg IM every 4 months, 45 mg IM every 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goserelin (Zoladex)</td>
<td>SC implant options: 3.6 mg SC every month, 10.8 mg SC every 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-androgens</strong></td>
<td></td>
<td>Hot flashes, edema</td>
<td>Avoid with severe hepatic disease</td>
<td>Metastatic prostate cancer</td>
</tr>
<tr>
<td>Bicalutamide (Casodex)</td>
<td>50 mg PO qd</td>
<td>Gynecomastia, hypertension, GI and CNS side effects, anemia, hepatotoxicity, rash. Uncommon: hypersensitivity reactions, pulmonary toxicity</td>
<td>Caution with diabetes. Substrate and inhibitor of CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td>250 mg PO tid</td>
<td>Gynecomastia, diarrhea, anemia, methemoglobinemia</td>
<td></td>
<td>Uncommonly used</td>
</tr>
<tr>
<td>Abiraterone (Zytiga)</td>
<td>1000 mg PO qd with prednisone 5 mg PO bid</td>
<td>Hepatotoxicity, hypertension, hypokalemia, arthralgia, myalgia, QT prolongation, diarhrea, dyspepsia, cough, arrhythmia, fracture, adrenal insufficiency, UTI</td>
<td>Decrease dose to 250 mg PO qd with moderate hepatic disease. Potent inhibitor of CYPs 1A2, 2D6, 2C8. Moderate inhibitor of CYPs 2C9, 2C19, 3A4/5</td>
<td>Advanced prostate cancer</td>
</tr>
<tr>
<td>Enzalutamide (Xtandi)</td>
<td>160 mg PO qd</td>
<td>Fatigue, diarrhea, hot flashes, musculoskeletal pain, headache, seizures, peripheral edema, dizziness, hematuria, paresthesia, hypertension</td>
<td>Caution with: seizure history, warfarin, drugs with narrow therapeutic index. Avoid potent CYP3A4 and CYP2C8 inducers and CYP2C8 inhibitors</td>
<td></td>
</tr>
<tr>
<td><strong>Gonadotropin-releasing hormone antagonist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degarelix (Firmagon)</td>
<td>240 mg SC. Then, in 28 days, give 80 mg SC every 28 days</td>
<td>QT prolongation, hypertension, injection site reactions, hot flashes, impotence, gynecomastia, insomnia, fever, hepatotoxicity, fatigue, weight gain, bone loss</td>
<td>Limited data with: severe hepatic disease, CrCl&lt;50</td>
<td>Metastatic prostate cancer</td>
</tr>
<tr>
<td><strong>Autologous cellular immunotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sipuleucel-T (Provenge)</td>
<td>50 million autologous CD54+ cells via IV infusion every 2 weeks for 3 doses</td>
<td>Acute infusion reactions, back pain, arthralgia, myalgia, headache, anemia,</td>
<td>Caution with: cardiac disease, pulmonary disease</td>
<td>Metastatic castration-resistant prostate cancer with no or minimal symptoms</td>
</tr>
</tbody>
</table>
# Prostate Cancer

<table>
<thead>
<tr>
<th>Antineoplastic agents</th>
<th>dizziness, asthenia</th>
<th>Hematologic toxicity, risk of infection or bleeding, vomiting</th>
<th>Metastatic castration-resistant prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel (Taxotere, Doceforz)</td>
<td>75 mg/m² IV every 21 days with prednisone 5 mg PO bid</td>
<td>Neuropathy, alopecia, edema, rash, dyspnea, injection site reactions, diarrhea, stomatitis, radiation recall reaction, hepatotoxicity</td>
<td>Increased mortality risk in certain patients. Risk of: neutropenia, severe hypersensitivity reactions, fluid retention. Extreme caution with hepatic disease. Must premedicate. Metabolized by CYP3A</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>12-14 mg/m² IV every 21 days with either hydrocortisone 20 mg every AM and 10 mg every PM, or prednisone 10 mg PO qd</td>
<td>Stomatitis, thinning of hair, injection site reactions, urine and nail discoloration, hepatotoxicity</td>
<td>Administer only by slow IV infusion and avoid extravasation. Monitor baseline neutrophils and CBC. Cardiotoxicity. Avoid with hepatic disease. Obtain baseline LVEF</td>
</tr>
<tr>
<td>Cabazitaxel (Jevtana)</td>
<td>25 mg/m² IV every 21 days with prednisone 10 mg PO qd</td>
<td>Diarrhea, nephrotoxicity, peripheral neuropathy, dizziness, fatigue, asthenia, dyspnea, fever, alopecia, infertility</td>
<td>Neutropenia, severe hypersensitivity reactions. Avoid with hepatic disease. Must premedicate. Substrate of CYP3A4 and P-gp</td>
</tr>
</tbody>
</table>

## Antiresorptive agents

<table>
<thead>
<tr>
<th>Antiresorptive agents</th>
<th>dizziness, asthenia</th>
<th>Hematologic toxicity, risk of infection or bleeding, vomiting</th>
<th>Metastatic castration-resistant prostate cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax)</td>
<td>70 mg PO weekly. Take on an empty stomach 2 hrs prior to breakfast, with 8 ounces water. Remain upright for at least 30 min</td>
<td>GI side effects, musculoskeletal pain, dizziness, edema, hypophosphatemia, atypical femur fractures with long-term use</td>
<td>Avoid with: CrCl&lt;35, esophageal irritation or stricture. Caution with: upper GI disorders, chronic anticoagulation</td>
</tr>
<tr>
<td>Denosumab (Prolia)</td>
<td>Osteoporosis: 60 mg SC every 6 months. Bone metastases: 120 mg SC every 4 weeks. Not for patient self-administration</td>
<td>Infection, rash, pruritus, hypercholesterolemia</td>
<td>Caution with CKD</td>
</tr>
<tr>
<td>Zoledronic acid (or zoledronate) (Reclast)</td>
<td>Osteoporosis: 4 mg IV every 3 months. Bone metastases: 4 mg IV every 3-4 weeks. Administer over at least 15 min</td>
<td>GI side effects, musculoskeletal pain, fever, flu-like syndrome, hypophosphatemia, nephrotoxicity, atypical femur fractures with long-term use</td>
<td>Avoid with CrCl&lt;35. May need to decrease dose with CrCl&lt;60</td>
</tr>
</tbody>
</table>

= first-line agent; = black box warning; AM = morning; bid = twice daily; CBC=complete blood count; CKD = chronic kidney disease; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P450 isoenzyme; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; im = intramuscular; iv = intravenous; LVEF = left ventricular ejection fraction; P-gp = P-glycoprotein; PM = evening; po = oral; qd = once daily; qid = four times daily; sc = subcutaneous; tid = three times daily; UTI = urinary tract infection.

PIER provides key prescribing information for practitioners but is not intended to be a source of comprehensive drug information.
## TNM Staging Classification of Prostate Cancer

<table>
<thead>
<tr>
<th>T1: No palpable disease on DRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a: Cancer discovered incidentally in less than 5% of the tissue resected during a TURP</td>
</tr>
<tr>
<td>T1b: Cancer discovered in more than 5% of the tissue resected during a TURP</td>
</tr>
<tr>
<td>T1c: Cancer detected on transrectal prostate biopsy specimens being performed due to an elevated PSA level</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T2: Palpable disease but no evidence of extracapsular extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2a: Cancer palpable on less than one half of one side of the gland</td>
</tr>
<tr>
<td>T2b: Cancer palpable on only one side but involving more than half of that side</td>
</tr>
<tr>
<td>T2c: Cancer palpable on both sides of the gland</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T3: Extracapsular extension or involvement of the seminal vesicles</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3a: Extracapsular extension</td>
</tr>
<tr>
<td>T3b: Seminal vesicle invasion</td>
</tr>
<tr>
<td>T4: Invasion of the bladder, rectum, or pelvic side wall</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N0: No pelvic lymph-node involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>NI: Pelvic lymph-node metastases</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M0: No distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1: Visceral or distant lymph-node metastases</td>
</tr>
</tbody>
</table>

DRE = digital rectal examination; PSA = prostate-specific antigen; TNM = tumor, node, metastasis; TURP = transurethral resection of the prostate.