

CARCINOMA OF THE PROSTATE

Incidence & Epidemiology

Prostate cancer is the most common cancer detected in American men. Although prostate cancer is the second leading cause of cancer death for men, mortality rates have been declining since the mid-1990s. Of all cancers, the prevalence of CaP increases the most rapidly with age. However, unlike most cancers, which have a peak age of incidence, the incidence of CaP continues to increase with advancing age. The lifetime risk of a 50-year-old man for latent CaP (detected as an incidental finding at autopsy, not related to the cause of death) is 40%; for clinically apparent CaP, 9.5%; and for death from CaP, 2.9%. Thus, many prostate cancers are indolent and inconsequential to the patient while others are virulent, and if detected too late or left untreated, they result in a patient's death. This broad spectrum of biological activity can make decision making for individual patients difficult.

Several risk factors for prostate cancer have been identified. As discussed above, increasing age heightens the risk for CaP. Which of the factors associated with the aging process are responsible for this observation is unknown. The probability of CaP developing in a man under the age of 40 is 1 in 10,000; for men 40–59 it is 1 in 103, and for men 60–79 it is 1 in 8. African Americans are at a higher risk for CaP than whites. In addition, African American men tend to present at a later stage of disease than whites. Controversial data have been reported suggesting that mortality from this disease may also be higher for African Americans. A positive family history of CaP also increases the relative risk for CaP. The age of disease onset in the family member with the diagnosis of CaP affects a patient's relative risk. If the age of onset is 70, the relative risk is increased fourfold; if the age of onset is 60, the relative risk is increased fivefold; and if the age of onset is 50, the relative risk is increased sevenfold. Although diagnostic biases exist between countries, differences in the incidence of prostate cancer are real. These differences may be related to differences in diet (Chan et al, 2005). Epidemiologic studies have shown that the incidence of clinically significant prostate cancer is much lower in parts of the world where people eat a predominantly low fat, plant-based diet. In addition, migrant studies demonstrate that when men from a low-risk country move to the United States and begin eating a westernized diet, their rates of prostate cancer increase severalfold and approach that of the host country. Total fat intake, animal fat intake, and red meat intake are associated with an increased risk of prostate cancer, whereas intake of fish is associated

with a decreased risk. There is considerable controversy on the impact of obesity on prostate cancer. Some studies suggest that obesity is associated with an increased risk of more advanced disease and a higher recurrence rate after treatment. Additionally, lycopene, selenium, omega-3 fatty acids (fish), and vitamin E intake have been shown to be protective, whereas vitamin D and calcium increase risk. Previous vasectomy has been suggested as a factor that heightens the risk for CaP, but these data are controversial.

Pathology

Over 95% of the cancers of the prostate are adenocarcinomas. Of the other 5%, 90% are transitional cell carcinomas, and the remaining cancers are neuroendocrine (“small cell”) carcinomas or sarcomas. This discussion will address only adenocarcinomas.

PIN and atypical small acinar proliferation (ASAP) are thought to be precursor lesions. Men found to have either lesion may be at an increased risk of prostate cancer and warrant repeat biopsy certainly if an extended- core biopsy was not performed initially. High-grade PIN (HGPIN) is characterized by cellular proliferations within preexisting ducts and glands, with nuclear and nucleolar enlargement similar to prostate cancer. However, unlike cancer, HGPIN retains a basal cell layer identifiable by immunohistochemistry.

Approximately, 60–70% of cases of CaP originate in the peripheral zone, while 10–20% originate in the transition zone, and 5–10% in the central zone. Although prostate cancer is most often thought to be multifocal, the use of widespread screening and extended biopsy techniques has resulted in the increasing detection of unifocal and smaller cancers.

The histology of the remaining 5% of prostate cancer is heterogenous, arising from stromal, epithelial, or ectopic cells. It is becoming increasingly evident that neuroendocrine differentiation may occur in response to prolonged androgen deprivation. This can be recognized by staining such tissue for neuroendocrine markers (chromogranin A, neuron-specific enolase) and/or by measuring such markers in serum.

Grading & Staging

The Gleason grading system is the most commonly employed grading system in the United States. It is truly a system that relies upon the low-power appearance of the glandular architecture under the microscope. In assigning a grade to a given tumor, pathologists assign a primary grade to the pattern of cancer that is most commonly observed and a secondary grade to the second most commonly observed pattern in the specimen. Grades range from 1 to 5. If the entire specimen has only one pattern present, then both the primary and secondary grade are reported as the same grade. The **Gleason score** or **Gleason sum** is obtained by adding the primary and secondary grades together. As Gleason grades range from 1 to 5, Gleason scores or sums thus range from 2 to 10. Well-differentiated tumors have a Gleason sum of 2–4, moderately differentiated tumors have a Gleason sum of 5–6, and poorly differentiated tumors have a Gleason sum of 8–10. Historically, tumors having a Gleason sum of 7 have sometimes been grouped with the moderately differentiated tumors and at other times with the poorly differentiated tumors. One point that needs to be clarified is that the primary Gleason grade is perhaps the most important with respect to placing patients in prognostic groups. This is most important in assessing patients with a Gleason sum of 7. Patients with a Gleason sum of 7 who have a primary Gleason grade of 4 (4 + 3) tend to have a worse prognosis than those who have a primary Gleason grade of 3 (3 + 4). Many clinical series have failed to distinguish between these two populations and, therefore, caution must be exercised in reviewing these series.

The TNM staging system for CaP is presented in Table 22–3 (American Joint Committee on Cancer, 1997). Note that with respect to the primary tumor categorization (T stage), the clinical staging system uses results of the DRE and TRUS, but not the results of the biopsy. Some examples to illustrate this staging system follow. If a patient has a palpable abnormality on one side of the prostate, even though biopsies demonstrate bilateral disease, his clinical stage remains T2a. If a patient has a normal DRE, with TRUS demonstrating a lesion on one side and a biopsy confirming cancer, his clinical stage is also T2a (using results of DRE and TRUS). A T1c cancer must have *both* a normal DRE and a normal TRUS.

Patterns of Progression

The pattern of CaP progression has been well defined. The likelihood of local extension outside the prostate (extracapsular extension) or seminal vesicle invasion and distant metastases increases with increasing tumor volume and more poorly differentiated cancers. Small and well-differentiated cancers (grades 1 and 2) are usually confined to the prostate, whereas large-volume (>4 cm³) or poorly differentiated (grades 4 and 5) cancers are more often locally extensive or metastatic to regional lymph nodes or bone. Penetration of the prostatic capsule by cancer is a common event and often occurs along perineural spaces. Seminal vesicle invasion is associated with a high likelihood of regional or distant disease. Locally advanced CaP may invade the bladder trigone, resulting in ureteral obstruction. Of note, rectal involvement is rare as Denonvilliers fascia represents a strong barrier.

Lymphatic metastases are most often identified in the obturator lymph node chain. Other sites of nodal involvement include the common iliac, presacral, and periaortic lymph nodes. The axial skeleton is the most usual site of distant metastases, with the lumbar spine being most frequently implicated. The next most common sites in decreasing order are proximal femur, pelvis, thoracic spine, ribs, sternum, skull, and humerus. The bone lesions of metastatic CaP are typically osteoblastic. Involvement of long bones can lead to pathologic fractures. Vertebral body involvement with significant tumor masses extending into the epidural space can result in cord compression. Visceral metastases most commonly involve the lung, liver, and adrenal gland. Central nervous system involvement is usually a result of direct extension from skull metastasis.

Clinical Findings

A. SYMPTOMS

Most patients with early-stage CaP are asymptomatic. The presence of symptoms often suggests locally advanced or metastatic disease. Obstructive or irritative voiding complaints can result from local growth of the tumor into the urethra or bladder neck or from its direct extension into the trigone of the bladder. Metastatic disease to the bones may cause bone pain. Metastatic disease to the vertebral column with impingement on the spinal cord may be associated with symptoms of cord compression, including paresthesias and weakness of the lower extremities and urinary or fecal incontinence.

B. SIGNS

A physical examination, including a DRE, is needed. Induration, if detected, must alert the physician to the possibility of cancer and the need for further evaluation (ie, PSA, TRUS, and biopsy). Locally advanced disease with bulky regional lymphadenopathy may lead to lymphedema of the lower extremities. Specific signs of cord compression relate to the level of the compression and may include weakness or spasticity of the lower extremities and a hyperreflexic bulbocavernosus reflex.

C. LABORATORY FINDINGS

Azotemia can result from bilateral ureteral obstruction either from direct extension into the trigone or from retro- peritoneal adenopathy. Anemia may be present in meta- static disease. Alkaline phosphatase may be elevated in the presence of bone metastases. Serum acid phosphatase may be elevated with disease outside the confines of the prostate.

D. TUMOR MARKERS—PROSTATE-SPECIFIC ANTIGEN

PSA is a serine protease produced by benign and malignant prostate tissues. It circulates in the serum as uncomplexed (free or unbound) or complexed (bound) forms. Normal PSA values are those < 4 ng/mL.

Current detection strategies include the efficient use of the combination of DRE, serum PSA, and TRUS with systematic biopsy. Unfortunately, PSA is not specific for CaP, as other factors such as BPH, urethral instrumentation, and infection can cause elevations of serum PSA. Although the last two factors can usually be clinically ascertained, distinguishing between elevations of serum PSA resulting from BPH and those related to CaP remains the most problematic. Serum PSA concentrations are decreased by treatment with agents that lower serum testosterone such as LHRH agonists and antagonists used to treat prostate cancer as well as with 5-alpha-reductase inhibitors used to treat BPH. Interestingly, serum PSA levels are decreased in men with high body mass indexes compared to normal weight men.

The positive predictive value of a serum PSA between 4 and 10 ng/mL is approximately 20–30%. For levels in excess of 10 ng/mL, the positive predictive value increases from 42% to 71.4%. Given that most men with elevated serum PSA levels do not have prostate cancer, there is great interest in identifying makers with greater sensitivity and/ or specificity.

Numerous strategies to refine PSA for cancer detection have been explored. Their common goal is to decrease the number of false-positive test results. This would increase the specificity

and positive predictive value of the test and lead to fewer unnecessary biopsies, lower costs, and reduced morbidity of cancer detection. Attempts at refining PSA have included PSA velocity (change of PSA over time), PSA density (standardizing levels in relation to the size of the prostate), age-adjusted PSA reference ranges (accounting for age-dependent prostate growth and occult prostatic disease), and PSA forms (free versus protein-bound molecular forms of PSA).

1. PSA velocity - PSA velocity refers to the rate of change of serum PSA. A retrospective study has shown that men with prostate cancer have a more rapidly rising serum PSA in the years before diagnosis than do men without prostate cancer. Patients whose serum PSA increases by 0.75 ng/mL/y appear to be at an increased risk of harboring cancer.

2. PSA density - PSA levels are elevated approximately 0.12 ng/mL/g of BPH tissue. Thus, patients with enlarged glands due to BPH may have elevated PSA levels. The ratio of PSA to gland volume is termed the PSA density. Some investigators advocate prostate biopsy only if the PSA density exceeds 0.1 or 0.15, while others have not found PSA density to be useful.

3. Age-adjusted reference ranges for PSA - it is thought that the rise in PSA with increasing age results from prostate gland growth from BPH, the higher incidence of subclinical prostatitis, and the growing prevalence of microscopic, clinically insignificant prostate cancers.

4. Racial variations in CaP detection - previously, it was noted that in men without prostate cancer, African American men presented with higher baseline serum PSA and PSA density. In addition, African American men had worse outcomes (cancer recurrence and mortality) compared to Caucasian, Hispanic, and Asian American men. Differential screening practices were recommended based on these results. However, more contemporary analyses suggest that these discrepancies are disappearing. In addition, much of any variation noted may be more strongly related to education, insurance status, and access to health care than ethnicity.

5. Molecular forms of PSA - the most recent refinement in PSA has been the recognition of the various molecular forms of PSA - free and protein-bound. Approximately 90% of the serum PSA is bound to alpha-1-antichymotrypsin, and lesser amounts are free or are bound to alpha-2-macroglobulins. In the latter form, no epitopes to the antibodies used in the current assays are available, while PSA bound to alpha-1-antichymotrypsin may have 3 of its 5 epitopes masked. Early studies suggest that prostate cancer patients demonstrate a lower percentage of free PSA than do patients with benign disease. A large multicenter study has reported that in men with a normal DRE and a total PSA level between 4 and 10 ng/mL, a 25% free PSA cutoff would detect 95% of cancers while avoiding 20% of unnecessary biopsies. The cancers associated with >25%

free PSA were more prevalent in older patients and generally were less threatening in terms of tumor grade and volume (Catalona et al, 1998).

E. PROSTATE BIOPSY

Prostate biopsy should be considered in men with an elevated serum PSA, a DRE, or a combination of the two.

Prostate biopsy is best performed under TRUS guidance using a spring-loaded biopsy device coupled to the imaging probe. Biopsies are taken throughout the peripheral zone of the prostate, rather than just sampling an area abnormal on the basis of DRE or TRUS. Traditionally, 6 (sextant) biopsies were taken along a parasagittal line between the lateral edge and the midline of the prostate at the apex, midgland, and base bilaterally. However, several investigators have shown that increasing the number (≥ 10) and performing more laterally directed biopsies of the peripheral zone will increase detection rates 14–20% over the more traditional sextant technique.

Prostate biopsy is usually performed using local anesthesia and preprocedure antibiotic prophylaxis. Although prostate biopsy is usually very well tolerated by patients, approximately 10 – 24% of those undergoing the procedure will find it very painful. The use of local anesthesia, either applied topically along the anterior rectal wall, injected into or adjacent to the prostate, or a combination of the two, decreases pain associated with the procedure. Hematospermia and hematuria are common occurring in approximately 40 – 50% of patients. Minor rectal bleeding may occur, as well. High fever is rare occurring in 2.9 – 4.2% of patients.

F. COMBINED MODALITY RISK ASSESSMENT

Nomograms and probability tables incorporating serum PSA, cancer grade, T stage, and cancer volume as assessed by extent of biopsies involved with cancer and patient age have been published, are widely used, and allow a better assessment of disease natural history (with or without treatment) and more appropriate selection of initial treatment.

Imaging

TRUS - TRUS is useful in performing prostatic biopsies and in providing some useful local staging information if cancer is detected. Almost all prostate needle biopsies are performed under TRUS guidance. This allows uniform spatial separation and sampling of the regions of the prostate and also makes lesion-directed biopsies possible. If visible, CaP

tends to appear as a hypoechoic lesion in the peripheral zone. TRUS provides more accurate local staging than does DRE. The sonographic criteria for extracapsular extension are bulging of the prostate contour or angulated appearance of the lateral margin. The criteria for seminal vesicle invasion are a posterior bulge at the base of the seminal vesicle or asymmetry in echogenicity of the seminal vesicle associated with hypoechoic areas at the base of the prostate.

Endorectal magnetic resonance imaging (MRI) - Use of an endorectal coil improves cancer detection and staging compared to the use of a standard body coil.

Axial imaging (CT, MRI) - Cross-sectional imaging of the pelvis in patients with CaP is selectively performed to exclude lymph node metastases in high-risk patients who are thought to be candidates for definitive local therapy, whether it be surgery or irradiation. Both MRI and computed tomography (CT) are used for this purpose. Analyses of several contemporary series of patients with clinically localized prostate cancer suggest that the risk of lymph node metastases is low and that its risk can be quantified on the basis of serum PSA, local tumor stage, and tumor grade.

Bone scan - When prostate cancer metastasizes, it most commonly does so to the bone. Soft tissue metastases (eg, lung and liver) are rare at the time of initial presentation. However, patients with PSA 15 ng/mL or greater, locally advanced disease (T3B, T4) are at higher risk for bone metastases and should be considered for bone scan.

Antibody imaging - ProstaScint is a murine mono- clonal antibody to an intracellular component of the prostate - specific membrane antigen (PSMA), which is conjugated to 111 indium.

Differential Diagnosis

Not all patients with an elevated PSA concentration have CaP. Other factors that elevate serum PSA include BPH, urethral instrumentation, infection, prostatic infarction, or vigorous prostate massage. Induration of the prostate is associated not only with CaP, but also with chronic granulomatous prostatitis, previous TURP or needle biopsy, or prostatic calculi. Sclerotic lesions on plain x-ray films and elevated levels of alkaline phosphatase can be seen in Paget's disease and can often be difficult to distinguish from metastatic CaP. In Paget's disease, PSA levels are usually normal and x-ray findings demonstrate subperiosteal cortical thickening.

Screening for CaP

The case for CaP screening is supported by the following: The disease is burdensome in this country; PSA improves detection of clinically important tumors without significantly increasing the detection of unimportant tumors; most PSA-detected tumors are curable; prostate cancer mortality is declining in regions where screening occurs; and curative treatments are available. If screening is undertaken, it appears that the use of both DRE and serum PSA is preferable to either one used alone. Although many recommend that screening be undertaken at age 50, some have advocated for earlier screening starting at age 40. Although annual screening is most often recommended. Some feel that men with very low serum PSA level (≤ 1 ng/ mL) may be able to be screened at less frequent intervals (every 2 or 3 years).

Screening should be undertaken in men who are healthy enough to benefit from it. Screening may be highly encouraged in certain populations with a higher disease prevalence and/or mortality such as African American men and those with a strong family history of the disease.

Treatment

LOCALIZED DISEASE

1. General considerations - The optimal form of therapy for all stages of CaP remains a subject of great debate. Treatment dilemmas persist in the management of localized disease (T1 and T2) because of the uncertainty surrounding the relative efficacy of various modalities, including radical prostatectomy, radiation therapy, and surveillance. Currently, treatment decisions are based on the grade and stage of the tumor, the life expectancy of the patient, the ability of each therapy to ensure disease-free survival, its associated morbidity, and patient and physician preferences. Until recently, there was little information to be sure that treatment of early stage disease had an important impact on overall and cancer-specific survival. A well-conducted randomized trial of radical prostatectomy versus surveillance in men with early stage prostate cancer was conducted in Scandinavia (Bill-Axelsson et al, 2005). Men who underwent radical prostatectomy were less likely to die, die of prostate cancer (risk reduction 0.56), develop metastases (risk reduction 0.60), or suffer local cancer progression (risk reduction 0.33) compared to men who underwent initial surveillance. The advantage to surgery was most apparent in younger patients.

2. Watchful waiting and active surveillance - Although local cancer progression may occur, with watchful waiting for early stage prostate cancer, disease-specific mortality at 10 years is low varying generally between 4% and 15%. However, in further follow-up

from 15 to 20 years, a substantial increase in the risk of local and systemic progression and death from prostate cancer may be seen (Johansson, Andren et al, 2004). The risk of progression is related significantly to cancer grade. The risk of progression is low in those with Gleason grades 2–6 (no pattern 4 or 5), but increases significantly for those with Gleason grades 7 through 10. Most of the men, in these previously reported series of men managed with watchful waiting, had palpable disease and, therefore, larger, more significant cancer than most of those detected currently based on serum PSA. In addition, most men were not followed carefully with periodic clinical, radiographic, and laboratory (PSA) reevaluation. They were treated, usually with androgen deprivation, when symptomatic metastatic disease was detected. A more modern concept of watchful waiting is better termed “active surveillance” where men with very well-characterized, early stage, and low to intermediate grade cancer are followed very carefully and treated at the first sign of subclinical progression based on serial and regular physical examinations, serum PSA measurements, and repeat prostatic biopsy (Klotz 2005).

3. Radical prostatectomy - Patients with organ-confined cancer have 10-year disease-free survival ranging from 70% to 85% in several series. Those with focal extracapsular extension demonstrate 85% and 75% disease-free survival at 5 and 10 years, respectively. Morbidity associated with radical prostatectomy can be significant and is in part related to the experience of the surgeon. Immediate intraoperative complications include blood loss, rectal injury, and ureteral injury. Blood loss is more common with the retropubic approach than with the perineal approach because in the former, the dorsal venous complex must be divided. Rectal injury is rare with the retropubic approach and more common with the perineal approach but usually can be immediately repaired without long-term sequelae. Ureteral injury is exceedingly rare with any technique. Perioperative complications include deep venous thrombosis, pulmonary embolism, lymphocele formation, and wound infection. Late complications include urinary incontinence and impotence. Potency can be improved with early use of PDE-5 inhibitors.

4. Radiation therapy - external beam therapy –

5. Radiation therapy - brachytherapy –

6. Cryosurgery and high-intensity focused ultrasound (HIFU) -

RECURRENT DISEASE

1. Overview - A substantial number of men who are treated with either surgery or radiation for presumed clinically localized prostate cancer will relapse based on evidence of a detectable or rising serum PSA after treatment, respectively. Biochemical failure may have a variable natural history after any kind of initial treatment and may signify localized disease, systemic disease, or a combination of the two. After either form of treatment, an interval to PSA failure <3–6 years and a posttreatment PSA doubling time <3 months place a man at increased risk for metastases and subsequent prostate cancer-specific mortality.

2. Following radical prostatectomy - The likelihood of recurrence following radical prostatectomy is related to cancer grade, pathologic stage, and the extent of extracapsular extension. Cancer recurrence is more common in those with positive surgical margins, established extracapsular extension, seminal vesicle invasion, and high-grade disease. For those patients in whom a detectable PSA level develops after radical prostatectomy, the site of recurrence (local versus distant) can be established with reasonable certainty based on the interval from surgery to the detectable PSA concentration, PSA doubling time, and selective use of imaging studies.

Patients with persistently detectable serum PSA levels immediately after surgery, those with PSA levels that become detectable in the early postoperative period, and those with serum PSA levels that double rapidly are more likely to have systemic relapse.

Those patients thought to have recurrent localized disease based on a long time from surgery to biochemical failure, prolonged PSA doubling times (>10–12 months), and presence of positive surgical margins at the time of surgery are most likely to benefit from salvage radiation (approximately 77% freedom from subsequent relapse). Those with high-grade disease or seminal vesicle involvement at the time of surgery, who fail early or with rapid PSA kinetics after surgery, are less likely to respond and should be considered for systemic therapy.

3. Following radiation therapy - A rising PSA level following definitive radiotherapy is indicative of cancer recurrence.

METASTATIC DISEASE

Initial endocrine therapy - Since death due to CaP is almost invariably a result of failure to control metastatic disease, a great deal of research has concentrated on efforts to improve control of distant disease. It is well known that most prostatic carcinomas are hormone dependent and that approximately 70–80% of men with metastatic CaP respond to various forms of androgen deprivation. Testosterone, the major circulating androgen, is produced by the Leydig cells in the

testes (95%), with a smaller amount being produced by peripheral conversion of other steroids. Although 98% of serum testosterone is protein bound, free testosterone enters prostate cells and is converted to dihydrotestosterone (DHT), the major intracellular androgen. DHT binds to a cytoplasmic receptor protein and the complex moves to the cell nucleus, where it modulates transcription. Androgen deprivation may be induced at several levels along the pituitary-gonadal axis using a variety of methods or agents. Use of a class of drugs (LHRH agonists) has allowed induction of androgen deprivation without orchiectomy or administration of diethylstilbestrol. There are 4 LHRH agonists currently approved by the FDA for the treatment of prostate cancer: goserelin acetate, triptorelin pamoate, histrelin acetate, and leuprolide acetate. These can be delivered by injection monthly or as depot preparations lasting 3–6 months. A subcutaneous implant that releases leuprolide acetate at a constant rate for 1 year is also available. An LHRH agonist (Abarelix, Praecis Pharmaceuticals) has been developed, as well. However, concerns about allergic reactions associated with administration have limited its development. Agonists would avoid the “flare” phenomenon associated with antagonists where serum testosterone concentrations increase before falling. Such an increase could cause symptoms in those with advanced cancer. Currently, administration of LHRH agonists is the most common form of primary androgen blockade used. Orchiectomy, once common, is much less commonly performed today. Estrogens achieve castration by feedback inhibition of the hypo- thalamic-pituitary axis and, perhaps, by a direct cytotoxic effect. Although effective, their use is limited due to an increased risk of negative cardiovascular effects. Because of its rapid onset of action, ketoconazole should be considered in patients with advanced prostate cancer who present with spinal cord compression or disseminated intravascular coagulation. Complete androgen blockade can be achieved by combining an antiandrogen with the use of an LHRH agonist or orchiectomy. Antiandrogens appear to act by competitively binding the receptor for DHT, the intracellular androgen responsible for prostatic cell growth and development. The timing of initial endocrine therapy in CaP has been an area of great debate for many years. Androgen deprivation is not without side effects including hot flashes, anemia, loss of libido and sexual function, loss of bone mineral density, increased weight and body fat, and cognitive changes. In addition, increases in total cholesterol, low- and high-density lipoproteins, and serum triglycerides have been reported. Men on androgen deprivation should be monitored for such side effects as treatment for most is readily available. Many men diagnosed with prostate cancer suffer from low bone mineral density, which can be exacerbated with androgen deprivation therapy. Many agents may prevent generalized and localized bone loss, including calcium and vitamin D supplements and, if significant, bisphosphonates. Anemia is usually mild, but may be managed with recombinant erythropoietin. Although there are a number

of treatments for men with hot flashes that are especially troublesome, medroxyprogesterone acetate (300– 400 mg IM monthly) is an effective treatment with limited side effects.

Manipulations for hormone refractory prostate cancer—Patients receiving complete androgen blockade therapy who demonstrate a rise in serum PSA levels are currently managed by discontinuing the antiandrogen. Some investigators have postulated that emergence of the hormone-refractory state results from mutations in the androgen receptor. Typically, antiandrogens competitively inhibit the androgen receptor, but it is possible that these agents actually stimulate a mutant androgen receptor. Removal of this stimulus (stopping the antiandrogen), thus leads to a secondary response. Patients receiving monotherapy (LHRH agonist or orchiectomy) whose PSA level starts rising may respond to the addition of an antiandrogen. Response rates are approximately 20–30% in this setting. In addition, use of ketoconazole, aminoglutethimide, corticosteroids, and estrogenic compounds should be considered, as a significant number of patients who have failed initial forms of androgen deprivation will respond to these agents. Although chemotherapy was once not thought to be very effective men with hormone refractory prostate cancer, two recent trials demonstrated a survival benefit for docetaxel-based therapy in men with hormone refractory prostate cancer.

Table 22–3. TNM Staging System for Prostate Cancer.

T—Primary tumor

Tx	Cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (PIN)
T1a	□ 5% of tissue in resection for benign disease has cancer, normal DRE
T1b	>5% of tissue in resection for benign disease has cancer, normal DRE
T1c	Detected from elevated PSA alone, normal DRE and TRUS
T2a	Tumor palpable by DRE or visible by TRUS on one side only, confined to prostate
T2b	Tumor palpable by DRE or visible by TRUS on both sides, confined to prostate
T3a	Extracapsular extension on one or both sides
T3b	Seminal vesicle involvement
T4	Tumor directly extends into bladder neck, sphincter, rectum, levator muscles, or into pelvic sidewall

N—Regional lymph nodes (obturator, internal iliac, external iliac, presacral lymph nodes)

Nx	Cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a regional lymph node or nodes

M—Distant metastasis

Mx	Cannot be assessed
M0	No distant metastasis
M1a	Distant metastasis in nonregional lymph nodes
M1b	Distant metastasis to bone
M1c	Distant metastasis to other sites

DRE, digital rectal examination; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.

Source: American Joint Committee on Cancer: *Cancer Staging Manual*, 5th ed. Lippincott-Raven, 1997.