Prostate Cancer, Hormone Treatment and Bone Health: Present Management and Future Directions

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1 Introduction

Prostate cancer is the most common organ cancer in men, with more than two million American men currently living with the disease. Approximately 16% of all men will be diagnosed with this malignancy during their lifetime. Most cancers are low grade (Gleason grade 6 or less) and carry a thirty percent chance of progression, some intermediate (Gleason grade 7) with those designated 4+3 being worse than those designated 3+4, and the remainder high grade (Gleason grade 8-10) with a high likelihood of life-threatening morbidity. Treatments for prostate cancer range from simply following the disease, as in watchful waiting or active surveillance, potentially curative treatments like surgery or radiotherapy, and palliative hormonal therapy.

Androgen deprivation therapy (ADT) has become the accepted treatment for patients whose cancer has spread beyond the gland or who have recurrent disease, after surgery or radiotherapy. ADT lowers the body’s ability to make and to respond to the male sex hormone, testosterone. Since testosterone is the most potent promoter of prostate cancer, regulating its production and limiting its effects on a cellular level are essential to controlling the progression of prostate cancer.

Side effects of ADT include hot flashes, anemia, and cognitive dysfunction, but what are most serious are the deleterious effects on bone health. ADT may lead to osteoporosis, predisposing castrated men to fractures and, ultimately, decreased survival.

This chapter will discuss the epidemiology, screening, diagnosis and treatment options of prostate cancer and its association with osteoporosis.

2 Epidemiology

Prostate cancer is the most common non-cutaneous malignancy in the United States. According to the American Cancer Society, men have a 16.7% lifetime risk of developing the disease, while the lifetime risk of death is approximately 2.6% (American Cancer Society, 2008).

African Americans are at higher risk than Caucasians, with a relative incidence of 1.6 (American Cancer Society, 2008). Family history is also a contributing factor.

Prostate cancer incidence peaked in 1992, and mortality has fallen steadily after the introduction of the blood test, prostate-specific antigen (PSA). PSA alone, however, does not fully explain the reduction in mortality from the disease during the last 30 years. Many clinicians believe that the reduction in mortality is due largely to the more aggressive treatment since the 1980s (Walsh, 2000). While rates of hormone therapy and observation strategies have remained stable since the 1980s, the rates of radical prostatectomy and radiation treatment have increased over the same time period (Stephenson, 2005). Today, the 5-year disease-specific survival for localized disease approaches 100%, and is 34% for men diagnosed with metastatic disease (American Cancer Society, 2008).

There is wide variation in the incidence of this malignancy among men of different nationalities. The incidence is higher in men who have immigrated to America compared to men who have stayed in their native country where the disease is less frequent. For example, Asian men living in the United States have a lower incidence than Caucasians, but their incidence is higher than age-matched men in Asia. These findings implicate environmental factors (Haenszel & Kurihara, 1968; Yu et al., 1991).

Many reasons have been proposed to account for the varying incidence among different population groups. Certain genes contribute towards tumor initiation, promotion and/or progression. Higher intake of
animal fat, higher body mass index (BMI), lower socioeconomic status and higher testosterone levels are all recognized factors. Differences in medical practice, like access to health care, rectal examinations, and PSA screening are all factors that influence the incidence of prostate cancer.

The lowest rate of prostate cancer is seen in the Far East and on the Indian subcontinent, while the highest rates occur in North America, Australia and Western Europe. Prostate cancer is the 5th most common malignancy worldwide, and second most common in men (Parkin et al., 2002). Mortality from prostate cancer is highest in the Caribbean nations (28 per 100,000 per year) and lowest in Southeast Asia, China and North Africa (<5 per 100,000 per year) (Parkin et al., 2002).

The strongest risk factor for prostate cancer is age. Prostate cancer is rare in men younger than age 50 (2% of all cases). The median age at diagnosis is 68 years, with 63% of all prostate cancers diagnosed after the age of 65, and the vast majority of mortalities occur in this age group (Ries et al., 1975-2007). Despite the widespread use of PSA, the average age of prostate cancer related death has remained stable since the late 1970s.

### 3 Screening

Screening for prostate cancer refers to the testing of healthy, asymptomatic men for the possibility of disease. For a screening test to be effective the disease entity must be prevalent in the general population, the test must be specific, sensitive, and cost effective. Furthermore, effective treatments must exist to affect outcomes. The goal of screening, after all, is to improve the overall health of the patient population by earlier diagnosis and earlier treatment

For prostate cancer, routine screening consists of regular rectal examinations and a PSA blood test. The benefits of screening for prostate cancer, however, are uncertain. Many studies have shown that screening reduces the number of men diagnosed at an advanced stage (van der Cruijsen-Koeter, 2006; Aus et al., 2007). However, the harm associated with treatments must be considered against the potential benefits.

#### 3.1 PSA

Prostate specific antigen is a member of the human glandular kallikrein family, known as human glandular kallikrein 3 (hK3). It, along with kallikrein 2, is one of the most widely studied members of the kallikrein family. So far, 15 functional kallikrein genes have been identified and extensive study of these markers has helped to improve the utilization of these markers. Other markers show promise and may improve on PSA as a screening tool for prostate cancer.

Mortality from prostate cancer has declined since the introduction of widespread PSA testing, with an absolute reduction of 32.5% since the early 1990s (SEER database) and a 75% reduction in the proportion of advanced disease at diagnosis. Two randomized trials that looked at prostate cancer-specific mortality in relation to PSA screening have been published, with contradictory results.

The European Randomized Trial of Prostate Cancer Screening (ERSPC) carried out PSA testing every 4 years and biopsied men with PSA counts over 4 ng/ml. This study reported a 20% reduction in prostate cancer-specific mortality in the screened population. Their screened cohort also had less high-grade cancer, less locally advanced cancer and less metastatic disease. The Prostate, Lung, Colon and Ovary (PLCO) study of the National Cancer Institute (NCI) in the United States initiated its study in 1993. Screening consisted of annual PSA testing, with PSA readings over 4 ng/ml triggering a prostate
biopsy. This study did not show any difference in prostate cancer specific mortality in the screened and unscreened population. It has been speculated that the unscreened population may have had PSA testing more often than admitted, contaminating the results. Despite the survival advantage of PSA screening demonstrated by the ERSPC trial, the study did show that 1410 men needed to be screened and 48 men treated to prevent one prostate cancer-related death (de Koning et al., 2002; Schroder et al., 2009; Andriole et al., 2009).

These two large trials have contributed important information regarding screening, such as frequency of testing and PSA cut-offs. Clearly, screening has led to a stage migration towards organ-confined disease and a reduction in patients diagnosed with advanced cancers. Unfortunately, these trials have also exposed the perils of screening, such as the overdetection of inconsequential disease and, possibly, overtreatment of prostate cancer. Information gathered from the prostate cancer prevention trial (PCPT) has shed light on the sensitivity and specificity of PSA screening in healthy men (Table 1).

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<tr>
<th>PSA</th>
<th>Cancer versus no cancer</th>
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<td>Sensitivity</td>
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*Table 1:* Sensitivity and specificity of PSA values in detecting prostate cancer (Thompson et al., 2004)

The National Comprehensive Cancer Network and the U.S. Preventive Services Task Force have published guidelines for prostate cancer screening. They concluded that PSA screening is inappropriate for men 75 years or older. More recently, advocates of screening have recommended screening for patients with at least a 10-year life expectancy (Lim & Sherin, 2008).

PSA cutoff values as an indication for prostate biopsy have changed to a more dynamic, spectrum-based practice. For example, the average annual increase of serum PSA ranges from 0.1 to 0.5 ng/ml in men with benign prostatic hyperplasia, related to a prostate growth of 1.8 ml/yr (Bonilla & McConnell, 1995).

The use of PSA escalation, or velocity, as an indication for biopsy has improved diagnostic accuracy. A PSA velocity that exceeds 0.75 ng/ml per year is associated with a higher rate of prostate cancer (Carter et al., 1992). Unfortunately, PSA velocity is not cancer-specific and varies significantly from day to day.

PSA density is the ratio of PSA value in relation to prostate volume, as measured by transrectal ultrasound (Benson et al., 1992). Normal prostatic epithelium contributes 0.1 ng/ml PSA per gram of tissue to the serum PSA level. That number jumps to 0.3 ng/ml for BPH (benign prostatic hyperplasia) tissue, and 3.5 ng/ml for prostate cancer epithelium. Variations in prostate volume measurement by different examiners and the variability between machines limit the accuracy of PSA density. In addition, the ratio of prostate stroma to epithelium varies from gland to gland (Partin et al., 1990). To date, the use of PSA density has not gained widespread acceptance as a screening tool.

Free to total serum PSA ratio has become an adjunctive assessment tool in determining the probability of cancer. PSA is either freely circulated in serum, or bound or complexed to protease inhibitors, notably, antichymotripsin (ACT) and macroglobulin (MG) (Christensson et al., 1993; Lilja, 1993; Stenman et al., 1994). Approximately 70% of serum PSA is bound to proteins. Free and total PSA can be de-
tected through immunoassays. Prostate cancer cells do not produce more PSA, per gram, than benign prostatic tissue. However, in the cancerous state, malignant cells may greatly outnumber those of benign stroma, while the PSA produced by malignant cells escapes proteolytic processing. Therefore, men with prostate cancer have a greater ratio of protein bound PSA and a lower percentage of free PSA, and can present with elevated levels of total PSA. The role of %fPSA is more applicable to PSA levels less than 10 ng/ml. A cutoff of <18% free/total ratio (0.18) improves the ability to diagnose cancer than total PSA readings (Christensson et al., 1993).

PSA is strongly affected by androgens (Young et al., 1991). However, PSA readings can be elevated by BPH, prostatitis, recent instrumentation, metabolic factors, and medications. The 5-alpha-reductase inhibitors can lower PSA by 50% after one year of use (Roehrborn et al., 2002). Medical treatments for prostate cancer, such as antiandrogens and luteinizing hormone releasing hormone (LHRH) agonists can profoundly reduce PSA levels. Surgery for BPH can reduce PSA levels, as well (Shingleton et al., 2000).

3.2 Digital Rectal Exam (DRE)

The addition of PSA to screening protocols has largely supplanted DRE as a prostate cancer screening test. DRE can miss many early cancers, and is seldom reproducible, even by experienced physicians (Catalona et al., 1997). Improved detection occurs when DRE and PSA are combined (Catalona et al., 1991) as the two tests detect different cancers (Okotie et al., 2007). Thus, DRE and PSA are considered complementary, and both tests should be offered simultaneously to screen for prostate cancer.

3.3 PCA-3

A unique non-coding RNA gene on chromosome 9, termed PCA-3, has been identified (Bussemakers et al., 1999). This protein, found in high concentrations in prostate tissue, is highly expressed in 95% of prostate cancers. Through PCR assays, investigators have found a 66-fold upregulation of this protein in prostate cancer tissue, compared to benign prostatic tissue samples. Additionally, the marker has been shown to be detectable in tissue samples with a paucity of cancerous tissue in a background of normal acini (de Kok et al., 2002). Thus, PCA-3 represents a potentially highly sensitive and specific biomarker for detecting prostate cancer. Sensitivities of up to 67% and specificities of up to 83% have been reported (Hessels et al., 2003).

With a negative predictive value of 90%, this test shows potential for reducing unnecessary and invasive biopsies and other costly diagnostic procedures. Unlike PSA, PCA-3 levels are unaltered by vigorous prostate massage or instrumentation. Thus the assay is performed on a urine sample collected after prostate massage. Finally, PCA-3 levels do not correlate directly with prostate volume, but have correlated well to prostate tumor volume (Whitman et al., 2008). PCA-3 shows promise by potentially removing the hazard of background biomarker elevation due to BPH or other benign processes, as is the case for PSA.

4 Diagnosis

Trans rectal ultrasound (TRUS) of the prostate was introduced in 1955 and was made popular in the 1970s (Watanabe et al., 1968). Then, in the 1980s, ultrasound-guided, spring-loaded needle biopsy of the prostate was introduced (Lee et al., 1989). A sextant biopsy template has largely been replaced by the
more extensive 10-16 biopsy template, reducing the undersampling and understaging of disease (Hodge et al., 1989; Stamey, 1995; Presti et al., 2003).

TRUS not only guides the needle into the desired area of the prostate to be sampled, but also provides information regarding prostate size, shape and tumor localization. Mild complications of TRUS biopsy of the prostate include hematuria and hematospermia, which usually resolve within 3-7 days (Rodriguez & Terris, 1998).

Antibiotic prophylaxis is mandatory to prevent serious infectious complications, but the choice of antibiotics and duration of coverage are controversial. A 3-day course of oral fluoroquinolone was shown to be no better than a single dose regimen (Kapoor et al., 1998; Sabbagh et al., 2004; Wolf et al., 2008). Despite antibiotic prophylaxis, post-biopsy infection rates vary between 0.7% and 4% (Webb et al., 1993; Aus et al., 1993).

The indications for recommending a prostate biopsy are controversial. Rather than classifying PSA values as “normal” or “abnormal”, the current view is that the risk of harboring prostate cancer is continuous as PSA values increase (Thompson et al., 2005). Even if a PSA value is deemed suspicious or elevated by the clinician, the PSA should be re-measured due to daily fluctuations in PSA levels.

4.1 MRI

Magnetic resonance imaging is gaining popularity when PSA readings are suspicious before invasive measures like needle biopsies are advised. The test is costly due to the special training that is required for accurate interpretation of the images.

5 Treatment

A comprehensive description of management strategies for localized, locally advanced and metastatic prostate cancers is beyond the scope of this chapter. We will discuss different treatment modalities their respective indications, risks and benefits.

5.1 Conservative Management

Historically, conservative management, that is, watchful waiting and active surveillance, are reserved for patients with life expectancies of more than 10 years and with low-risk features (i.e. low Gleason Grade, small volume disease, PSA<10). The term ‘watchful waiting’ refers to delayed treatment of disease until it manifests clinically, with little to no intervening follow-up. Active surveillance, on the other hand, mandates close follow-up and constant re-evaluations. This consists of PSA testing every 6 months and an annual biopsy. Active surveillance has been advised for younger patients with low to intermediate grade cancer in recent times. While attempts to better define aggressive and non-aggressive disease are ongoing (Epstein et al., 1994; Epstein et al., 1998; Kattan, 2003), several observation protocols have been suggested, but consensus is lacking (Zietman et al., 2004; Choo et al., 2002; Klotz, 2004; Patel et al., 2004; Dall’Era et al., 2008).

Watchful waiting has been reserved for patients who are too unwell to undergo definitive management, or have medical comorbidities and/or projected lifespan of less than 10 years. Two recent studies randomized patients to watchful waiting or radical prostatectomy, with conflicting results (Bill-Axelson et al., 2008; Wilt et al., 2012).
Prostate cancer commonly follows an indolent course. The median time from PSA failure after radical prostatectomy to bone metastases is 8 years, and the time to the development of bone metastases and death is another 5 years (Pound et al., 1999). Thus, watchful waiting or active surveillance are considered valid options for select patients.

5.2 Radical Prostatectomy

Radical prostatectomy was first reported by the German, Kuchler in 1866 (Kuchler, 1866), then by Young in 1905 (Young, 1905), and remains the gold standard for the treatment localized prostate cancer, with cure rates exceeding those obtained by radiation, castration or chemotherapy.

Since the widespread utilization of PSA as a screening test, more patients are being diagnosed with localized disease, thus improving the efficacy of radical prostatectomy (Moul et al., 2002).

Radical prostatectomy has evolved, with the open retropubic and perineal technique challenged by the minimally invasive (laparoscopic and robotic) techniques. In skilled hands, radical prostatectomy can be curative regardless of approach, with minimal damage to surrounding tissues (Hull et al., 2002). Radical prostatectomy involves the complete removal of the prostate gland along with the regional lymph nodes in selected cases with higher grades and elevated PSA.

The advantages of surgery are numerous, and include:

- Accurate tumor staging because the pathologist can examine the entire gland.
- PSA values after radical prostatectomy should fall to undetectable levels. Any rise in PSA post-operatively denotes disease recurrence.
- Patients with residual or recurrent disease can be treated with radiotherapy (Trock et al., 2008).

Disadvantages to radical prostatectomy include:

- The need for hospitalization and a significant recovery period.
- Erectile dysfunction, depending on the degree of nerve-sparing
- Urinary incontinence
- Failure to cure
- Risk of rectal injury

There has been a major shift towards the robotic-assisted approach in the past decade. This has occurred with little scientific data to support it and represents a major marketing success story. Different studies reported no advantages to the robotic approach (Smith, 2004; Wood et al., 2007), while another suggested higher recurrence with this novel technique (Hu et al., 2008).

Radical prostatectomy is a viable option in patients who have failed radiation or focal therapy. Surgery in this setting, though, is associated with increased technical difficulty and higher complication rates (Sanderson et al., 2006). Ideally, candidates for radical prostatectomy should be in good health, have a life expectancy of over 10 years and have significant cancer that can be completely removed.

5.3 Radiation Therapy

Radiotherapy is an effective and less invasive method to treat prostate cancer. Several forms of radiation therapy have been described, and different modalities are currently used worldwide. External beam radio-
therapy involves gamma radiation directed at the prostate. Three dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiation therapy (IMRT) are sophisticated methods for aiming radiation at complex geometric structures while sparing surrounding tissues, thus minimizing side effects of the treatment.

Adequate cancer control after radiation treatment is more difficult to define because not all prostate cells are eliminated and undetectable PSA readings are not expected. Despite the differences in outcome assessment, cancer control rates are comparable between radiation and radical prostatectomy (Gretzer et al., 2002). 76 to 80 Gray are commonly used, and this dose escalation has been shown to improve cancer control (Pollack et al., 2000).

Side effects from radiation treatment arise when surrounding structures absorb radiation. Specifically, the bladder, rectum, urinary striated sphincter and urethra are most commonly affected. Urinary incontinence is uncommon, but approximately 50% of treated patients develop erectile dysfunction after radiotherapy. For those patients with high risk or locally advanced disease at the time of diagnosis, several studies show a benefit from combined radiation therapy and androgen deprivation therapy (Bolla et al., 2002).

Assessing the success of cancer control can be challenging. PSA levels gradually decrease up to 2 to 3 years after the completion of radiation treatment. Inflammatory flares in the gland during the first two years after treatment can produce spikes in PSA values, called the PSA “bounce”, and complicate interpretation of post-radiation PSA values (Critz et al., 2000).

The American Society of Therapeutic Radiology and Oncology (ASTRO) define 3 consecutive PSA increases at 6-month intervals as a recurrence of disease. Cancer progression is defined as the half-way date between the PSA nadir and the first rising PSA reading. More recently, the Phoenix criterion, defined as a PSA rise of 2 ng/ml above nadir, has proven to be a more robust marker of post-radiotherapy biochemical recurrence and long-term survival (Abramowitz et al., 2008).

5.4 Brachytherapy

Brachytherapy involves the implantation of radioactive “seeds” or needles directly into the prostate gland. Under ideal conditions, this method delivers a high dose of extremely localized radiation, with minimal effect to surrounding structures. Seeds of the radioactive isotopes Iodine-125 and Palladium-103 are used; iodine for the less aggressive cancers and Palladium for the more aggressive malignancies.

While potentially efficacious, the treatment is less successful in patients with high prostate gland volumes because seed implantation is more difficult in larger glands. Often, patients with large glands are treated with ADT prior to seed implantation. Cancer control is excellent with this modality, using the ASTRO criteria (Ragde et al., 2001). Urinary side effects and erectile dysfunction are more common with brachytherapy than with external beam radiotherapy. However, rectal injury and proctitis are less with brachytherapy.

5.5 Adjuvant Radiotherapy Post Radical Prostatectomy

Surgery, followed by radiation is used for patients with adverse findings on the radical prostatectomy specimen, such as positive margins or capsular involvement. Radiotherapy is recommended, as well, for PSA recurrence, that is, PSA readings over 0.2 ng/ml after radical prostatectomy and rising (Leibovitch et al., 2000; Trock et al., 2008). Patients with seminal vesicle involvement and/or positive lymph nodes may also benefit from adjuvant radiation treatment (Cozzarini et al., 2004).
5.6 Cryoablation

When tissues are frozen the cells die. Cryoablation uses this principle to destroy prostate tissue, specifically, prostate cancer cells. Current technology freezes the entire gland using argon gas passed through hollow needles inserted directly into the prostate. Warm helium gas is passed through the urethra to protect the urethral mucosa during the procedure.

Cryoablation is used as primary treatment or as a salvage procedure for patients who have failed other treatments. ASTRO criteria are used to assess the success of cryoablation. There is, however, no consensus on the definition of biochemical failure after cryotherapy (Long et al., 2001). Current practice involves two cycles of freezing/thawing the prostate to -40°Celsius. The cytotoxic and antineoplastic effects of cryotherapy occur via several mechanisms:

- Mechanical – ice crystal formation and shear stress on cell membranes
- Biochemical – pH changes, osmolarity and electrolyte concentration changes
- Ischemic – blood stasis and thrombosis, disrupting blood supply
- Apoptotic – programmed cell death in injured but not killed cells
- Immunologic – antitumor immune response through the release of antigens

The advantages of cryoablation are that it is minimally invasive, it can be effectively repeated, there is no ionizing radiation involved and potency can be (although rarely is) preserved (Asterling & Greene, 2009). The most common complication is urinary incontinence (Pisters et al., 1999).

Long-term data regarding the efficacy, survival and quality of life outcomes of patients undergoing primary or salvage cryoablation are not yet available.

5.7 High-Intensity Focused Ultrasound (HIFU)

HIFU involves heating, rather than cooling the prostate (as in cryoablation) in order to destroy prostate tissue. Temperatures can reach as high as 100°Celsius. Cell death occurs days to months after the initial treatment through coagulative necrosis (Chapelon et al., 1999). The rectum is cooled during the procedure to minimize collateral damage from the heating probes. The most common complication is erectile dysfunction, and urinary retention. Patients often have a suprapubic catheter inserted before or during the procedure. Initial results are promising, but, as with cryoablation, long-term data is lacking.

6 Hormone Therapy for Prostate Cancer

Since the landmark research by Huggins in the 1940s, ADT remains one of the most durable treatment modalities for any known cancer. The development, growth and maintenance of the prostate gland are dependent on androgens. The arrival of androgens into the circulation begins with the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus in a pulsatile manner. The next step in the cascade is the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. LH acts directly on the Leydig cells in the testis to synthesize testosterone.
Testosterone circulates in the blood, largely bound to sex-hormone binding globulin (SHBG) and to albumin. Testosterone is also bound to corticosteroid-binding globulin, but with much less affinity. Approximately 97% of circulating testosterone is protein bound, while less than 3% is unbound. However, it is the unbound form of testosterone that is bioavailable (Debes & Tindall, 2002).

Once in the prostate, testosterone is converted to the more biologically active dihydrotestosterone through the enzymatic action of 5-alpha-reductase (5-AR). Of the two types of 5-AR, type 2 is the isoform that is in greatest concentration in the prostate. The testis produces more than 95% of circulating androgens. Androgens are also produced by the adrenal glands, but they are considered to be inconsequential to the growth and maintenance of prostatic tissue. On the receptor end of the equation lies the androgen receptor (AR). The AR is a cytoplasmic monomer, that when bound to DHT, dimerizes and translocates to the nucleus, acting as a transcription factor.

Androgens and the AR are essential to the regulation of apoptosis in prostate tissue. The presence of the androgen inhibits the enzymatic cascade that leads to programmed cell death, and up-regulates the antiapoptotic pathways (Kimura et al., 2001; Lu et al., 1997). In addition, castration limits angiogenesis by inhibiting both vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) (Joseph et al., 1997). Thus, inhibitions of androgens through either upstream (hypothalamic) or downstream (AR) targets are recognized mechanisms for inhibiting the growth and progression of prostate cancer. All current forms of ADT reduce the ability of androgens to activate the AR. However, when mutated, the AR can escape the normal, regulatory influences of the hormonal milieu. In prostate cancer, AR mutations can lead to androgen independent prostate cancer growth and progression, despite castration.

6.1 Mechanisms of Androgen Blockade

There are four methods of androgen blockade that are in clinical use:

1. Androgen source ablation
2. Inhibition of androgen synthesis
3. Androgen receptor blockade
4. Inhibition of the hypothalamic/pituitary axis

Side effects of castration are common to all of the above methods, including loss of libido, erectile dysfunction, decreased energy, gynecomastia and hot flushes. The development of osteopenia and osteoporosis as a result of castration and fractures associated with bone metastases will be discussed later.

1. Androgen Source Ablation

Bilateral orchiectomy is a quick and effective method for removing all biologically active androgens from the circulation. Within 24 hours of bilateral orchiectomy, serum testosterone levels are reduced by over 90% (Maatman et al., 1985). However, testosterone that is produced by the prostate, itself is not halted by orchiectomy, and is a potential contributor to eventual prostate cancer progression in this setting.

2. Inhibition of Androgen Synthesis

Several compounds halt the body’s production of endogenous testosterone. Ketoconazole is a broad-spectrum antifungal agent. However, it also inhibits a key enzymatic step in steroid production by preventing the conversion of lanosterol to cholesterol. As cholesterol is the building block for all steroid
hormones, blocking this enzymatic step is extremely effective at rapidly lowering testosterone levels. The response is not durable, with testosterone levels rebounding to normal ranges within 5 months of therapy (Vanuytsel et al., 1987). Ketokonazole is effective during bony pain crises in men with castrate resistant prostate cancer, but its long-term durability as a sustainable treatment is limited.

Abiraterone inhibits the enzyme cytochrome P17, a key and early enzyme in sex hormone synthesis. In addition to suppressing sex hormone synthesis, the compound also suppresses mineralcorticoids such as aldosterone, and glucocorticoids, such as cortisol. Accordingly, concurrent administration of exogenous steroids (e.g. prednisone) is prescribed when commencing abiraterone therapy.

3. Androgen Receptor Blockade

Cyproterone acetate, one of the first antiandrogens described and lowers testosterone levels by 70%-80% (Jacobi et al., 1980; Barradell & Faulds, 1994). Its use is limited, however, because of severe cardiovascular complications in 10% of patients (de Voogt et al., 1986).

Non-steroidal antiandrogens are widely used in current clinical practice. The common drugs in clinical use are Flutamide, Bicalutamide and Nilutamide. Because these compounds block the AR, the normally active negative feedback loop to the hypothalamus is disrupted. Thus, men treated with any of the above drugs have elevations in serum testosterone. This is clinically important, as men treated with these drugs are theoretically able to preserve potency. However, clinical trials have failed to demonstrate meaningful preservation of erectile function compared to patients undergoing orchiectomy (Schröder et al., 2000).

Bicalutamide is the most extensively studied non-steroidal antiandrogen, and at doses of 150 mg daily, has been shown to improve survival in men with metastatic prostate cancer comparable to bilateral orchiectomy (Wirth et al., 2005; McLeod et al., 2005).

4. Inhibition of the hypothalamic/pituitary axis

The use of an LH-RH agonist seems counterintuitive, as the product will stimulate androgen production, in what has been called the androgen flare (Waxman et al., 1985). However, with continued activation, the LH-RH receptors become desensitized, halting the production of LH, which leads to castrate levels of testosterone. There are 4 widely studied LH-RH analogues: Leuprolide, Goserelin, Triptorelin and Histrelin. In a meta-analysis, patients who received an LH-RH analogue had similar outcomes as patients undergoing orchiectomy (Seidenfeld et al., 2000).

To offset the initial rise in serum testosterone after initiating an LH-RH agonist, an anti-androgen is prescribed for 2 weeks prior to the administration of the agonist (Schultz & Senge, 1990). To avoid the negative consequences of the androgen flare, LH-RH antagonists (e.g. Abarelix, Degarelix) have been developed. These compounds competitively bind the LH-RH receptor in the pituitary and their administration precipitates a rapid decline in LH and circulating testosterone within 72 hours.

6.2 The Androgen Withdrawal Phenomenon

The androgen withdrawal phenomenon is a clinical observation when patients are treated with concurrent LH-RH agonist and an antiandrogen. Patients with a rising PSA despite combination therapy maybe benefit with a PSA decline of approximately 50% when the antiandrogen is withdrawn. This phenomenon is observed in approximately 15%-30% of patients (Kelly & Scher, 1993; Small & Srinivas, 1995).

6.3 Bone-Related Complications of Androgen Blockade
Androgen deprivation therapy (ADT) is associated with multiple adverse events, including hot flashes, gynecomastia, sexual dysfunction, decline in cognitive function, increased BMI and, most importantly, mortality from cardiovascular disease. This chapter, however, will focus on bone-related events associated with metastatic prostate cancer and medical castration, which is a source of major morbidity to the patient.

7 Bone Metastases in Advanced Prostate Cancer

There are two major cells that determine the strength and regulation of bone turnover: osteoclasts and osteoblasts. The primary function of the osteoclast is to break down bone, while the osteoblast functions to form new bone. Together, their concerted functions continuously remodel and reshape the skeleton. Osteoclasts migrate to an area of bone, resorb it, initiate apoptosis and allow for new bone formation by osteoblasts.

Prostate cancer preferentially spreads to bone, forming mainly osteoblastic lesions. Post-mortem studies have found that more than 80% of men who die from prostate cancer have bone metastases at autopsy (Harada et al., 1992). Typically, Patients with bone metastases present with pain. With advanced metastatic disease, vertebral lesions can compress the spinal cord, leading to nerve root compression, or cauda equina syndrome. Pathological fractures to the vertebrae are common consequences of metastatic disease. Finally, ADT contributes to osteoclast activity in men with prostate cancer, accelerating bone turnover and leading to an increased risk of fractures.

7.1 Androgen Deprivation Therapy (ADT) and Osteoporosis

As men age, they become pre-disposed to bone mineral loss and pathological fractures. In the patient with locally advanced or metastatic prostate cancer, ADT can intensify the process of bone loss and worsen the risk of fracture in an already vulnerable patient population. ADT leads to decreased bone mineral density (BMD) and, eventually, patients receiving ADT develop osteopenia – a decrease in BMD compared to an age-matched mean, or osteoporosis – defined as more than 2.5 standard deviations below an age-matched mean. Depending on the castration strategy and the patient population, bone mineral loss occurs at about 3% to 5% in the first year on ADT. Osteoporosis is common after 4 years of ADT (Wei et al., 1999). Other studies have shown that after 15 years, the cumulative incidence of pathological fractures was 40% in men treated with ADT, and 19% in non-castrated men (Melton et al., 2003). As our understanding of the short and long-term effects of ADT has grown, so has our need to develop countermeasures to preserve bone health in men receiving ADT.

8 Prevention of fractures

8.1 Recognition

BMD is the measuring stick for bone health in both men and women. While the gold standard for assessing BMD is histomorphometry (Humadi et al., 2010), several imaging techniques are available to estimate the BMD in men with hormone treated prostate cancer. These modalities include quantitative computerized tomography (CT), quantitative radiography, single x-ray absorptiometry and ultrasound. However, dual energy x-ray absorptiometry (DEXA) has become the most common measuring tool be-
cause of several advantages. Firstly, scores are reported as World Health Organization T-scores. Secondly, DEXA predicts future fracture risks. Finally, DEXA can accurately determine response to treatment (Blake & Fogelman, 2010). All men on long term ADT should undergo baseline and follow-up BMD testing (Bae & Stein, 2004; Diamond et al., 2004).

9 Current Prevention and Treatment Strategies

Bone fractures are a major source of morbidity and can lead to mortality in men treated with ADT. Accordingly, preventative measures, such as supplemental calcium and vitamin D, are recommended by the National Institute of Health (Michaelson et al., 2008). Bisphosphonates are a class of medications that have been long-used in the prevention of fractures in post-menopausal women with osteoporosis. Recent evidence suggests that the bisphosphonates offer protection to men on ADT, as well by reducing bone resorption through inhibiting osteoclast activity. The bisphosphonates pamidronate and alendronate showed increased prevention of osteoporosis compared to a placebo and even reversed bone loss in men on ADT (Smith et al., 2001; Greenspan et al., 2008).

Zoledronic acid is an intravenously administered bisphosphonates with potent anti-osteoclastic properties. In 2002, it was approved for the treatment of hypercalcemia and osteopenia in women (Green & Rogers, 2002). In 2004, the drug was approved for use in men on ADT and with bony metastases, and has been shown to prevent skeletal-related adverse events in this patient population (Saad et al., 2004).

Patients treated with zoledronic acid can experience fatigue, anemia, weakness, mild renal dysfunction and myalgia. Additionally, patients receiving this drug are at risk for developing osteonecrosis of the mandibular bone, called osteonecrosis of the jaw (ONJ). Thus patients are advised to undergo a dental evaluation before starting this treatment, especially those with a history of dental disease or poor overall dentition.

Another class of drugs, the receptor activator of nuclear factor \(\kappa\)B ligand (RANKL) inhibitors, interacts with the microenvironment of bone marrow to suppress osteoclasts. RANK is a receptor found on the cell surface of osteoclasts, and RANKL is its ligand. Inhibition of RANKL by the monoclonal antibody denosumab has been evaluated in several phase 3, placebo-controlled trials. Results showed superiority over zoledronic acid in delaying skeletal-related events in men with castration-resistant prostate cancer (CRPC) (Lipton et al., 2012).

As with zoledronic acid, denosumab produced side effects, including fatigue, nausea, hypocalcemia and ONJ. Men receiving zoledronic acid or denosumab should receive supplemental calcium and vitamin D. While denosumab does not require periodic renal function monitoring, serum calcium must be tested regularly.

9.1 Estrogens

Since the landmark study of Charles Huggins in 1941 (Huggins & Hodges, 1941), estrogens have had a longstanding role in the treatment of advanced prostate cancer. A direct correlation between serum levels of estrogen and bone density in men has been established (Slemenda et al., 1997). Ironically, though, the exact mechanism of action of estrogen on prostatic tissue is unknown. Estrogens act centrally, inhibiting LHRH secretion from the hypothalamus, halting testicular production of testosterone. At higher concentrations, estrogens competitively block prostate cancer androgen receptors. Historically, the most commonly used and studied estrogen is the synthetic estrogen, diethylstilbestrol (DES)
DES is a synthetic ethinyl estrogen. It exerts a negative feedback effect on the hypothalamus, decreasing LH secretion and, consequently, decreases androgen secretion by the testis. In addition, DES indirectly upregulates the secretion of sex hormone binding globulin and stimulates pituitary prolactin secretion. Thus, DES is very effective at shutting down testicular androgen secretion and causes castration (Robinson & Thomas, 1971; Malkowicz, 2001). Recent evidence suggests that DES exhibits high affinity for the AR and could modulate the course of prostate cancer (Wang et al., 2010).

In early studies in the 1970s by the Veterans Administration Cooperative Urological Research Group (VACURG), daily administration of 5 mg of DES was as effective as orchiectomy at achieving castrate levels of testosterone. Unfortunately, as this dose, a large number of patients experienced significant cardiovascular complications (Blackard et al., 1970).

Estrogen replacement has been used to prevent osteoporosis in women for decades. For men receiving ADT, the use of estrogen might seem an intuitive answer to combat pathological fractures. However, due to cardiac and thromboembolic complications, estrogen as a treatment for prostate cancer and as a preserver of bone health has fallen out of favor in urologic practice. While 5 mg of DES daily may carry significant cardiovascular and thromboembolic risks, other studies, using lower doses of DES, have shown promising results with less associated morbidity.

In the late 1990s, Smith and colleagues conducted a small pilot study, consisting of 21 men and administered 1 mg of DES daily to men with advanced prostate cancer. No blood thinners were used. Adverse thromboembolic events were observed in only 1 patient (Smith et al., 1998).

Jazieh and colleagues placed 14 men with advanced, castrate resistant prostate cancer on 3 mg of daily DES. They also administered warfarin concurrently in sufficient doses to achieve an international normalized ratio (INR) between 1.8-2.0. Interestingly, no thromboembolic events were noted in any of the study participants (Jazieh et al., 1994). Then, a phase 1-2 study conducted by Klotz and colleagues enrolled 32 men with advanced prostate cancer to receive both 2-3 mg daily of DES plus 1 mg warfarin, a commonly used blood thinner. While the outcomes of the study were geared towards PSA response to estrogen therapy, 28% of the study participants experienced a thromboembolic event (Klotz et al., 1999). However, warfarin doses were not titrated to an international normalized ratio (INR) between 2 to 3, which is considered to be an acceptable therapeutic range.

Researchers have found conclusive evidence that estrogens help to preserve bone density in men (Vandenput & Ohlsson, 2009). While zoledronic acid and denosumab are promising medications to prevent adverse bone events in men with advanced prostate cancer, they are expensive, require intravenous or subcutaneous injections, and can cause significant side effects. Estrogen can be taken orally and is inexpensive. In addition, there has been resurgence in research geared towards estrogen as a potential treatment for advanced prostate cancer. It is our belief that estrogen replacement therapy warrants further investigation as a potential adjunct for men on ADT in order to preserve and promote bone health, despite castration.

Alternative estrogen-related treatments for prostate cancer are the selective estrogen receptor modulators (SERMs). These compounds act as either estrogen receptor agonists or antagonists, depending on the biochemical milieu and presence of certain co-regulators. One of the SERMs, Toremifene, has been shown to decrease circulating testosterone levels by suppressing the hypothalamic-pituitary axis (Taneja et al., 2006). Perhaps the most interesting potential application of Toremifene is for chemoprevention of prostate cancer. High-grade prostatic intraepithelial neoplasia (PIN) is considered by many to be a premalignant precursor to prostate cancer, and this patient population could be an attractive target for chemoprevention strategies. In a multicentered, double-blind study, 514 men with high grade PIN and no
evidence of cancer on TRUS biopsy were given 20 mg of daily oral Toremifene, taken for 6-12 months. Results showed a significant reduction in the incidence of prostate cancer in the treatment group, compared with placebo (Price et al., 2006). However, in a larger double-blind study, involving 1590 men, 20 mg of daily Toremifene showed no overall risk reduction of developing prostate cancer, and no disease-specific survival benefit (Taneja et al., 2013).

Since the initial studies of Huggins and the VACURG, effective blood thinners have been approved and are prescribed to millions of North Americans for the prevention of thromboembolic events. The future of DES, other synthetic estrogens and SERMs in the context of ADT for advanced prostate cancer will likely prompt randomized controlled trials comparing low dose DES in combination with an effective blood thinner, such as warfarin, acetylsalicylic acid (ASA) and/or clopidogrel, to currently approved medications, such as alendronate, zoledronic acid and denosumab.

If the safety and efficacy of estrogen can be demonstrated, it could become, once again, another weapon in the urologist’s armamentarium against the morbidity associated with advancing prostate cancer and its therapies.

10 Summary

Prostate cancer is a common disease among older men. While most low-grade cancers display an indolent, non life-threatening course, other, higher-grade cancers are more aggressive and can be life threatening without treatment.

Screening for prostate cancer is controversial. However, mortality from prostate cancer has plummeted since the introduction of PSA into mainstream practice. The downside of PSA screening is overdiagnosis and overtreatment of some cancers.

Therapeutic options for prostate cancer range from non-invasive radiotherapy, to minimally invasive surgical procedures. In most instances, cure rates are high for localized disease. Should prostate cancer extend beyond the gland, or recur after definitive therapies such as surgery or radiotherapy, ADT is considered and initiated. Side effects of ADT are not benign, and osteoporotic fractures are a major source of morbidity in this patient population.

While estrogen was once considered a first line hormonal therapy for prostate cancer, its use has fallen out of favour due to the high incidence of thromboembolic events associated with its use. Fortunately, new blood thinners could re-ignite the use of low dose estrogen for the prevention of ADT-related fractures. More studies are necessary to determine the safety and efficacy of low dose estrogen to preserve bone health in men with advanced prostate cancer receiving ADT.

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