Prostate Cancer Bone Metastasis

5

Jonathan D. Tward

Introduction

Prostate cancer is the leading cancer diagnosis in American men, with 1 in 8 persons being diagnosed within their lifetimes. In 2014, it is estimated that about 233,000 persons will be diagnosed with prostate cancer, and that 29,480 will die of the disease [1]. There is controversy regarding the benefits of both screening and treatment of prostate cancer, as many prostate cancers currently diagnosed by prostate-specific-antigen (PSA) serum testing would have remained clinically occult throughout a man's lifetime. Nevertheless, prostate cancer remains the second-leading cause of cancer-related death in Western countries [2]. Although serum PSA levels are a controversial when used as a screening test, this tumor marker is an outstanding test at evaluating the treatment response of men undergoing various oncologic therapies.

The consequences of therapy and the direct impact of bone metastases on quality of life are significant for men living with prostate cancer. "Skeletal-related events" (SREs) is a defined term that has been adopted by the oncologic community, and is useful in comparing the efficacy of therapies on progression and impact on patient quality of life in research studies. The National Comprehensive Cancer Network (NCCN) task force defined SREs as "a constellation of skeletal complications, including fracture, need for surgery on bone, need for radiation to bone, spinal cord compression, and in some situations, hypercalcemia of malignancy" [3].

One universally accepted care standard in men diagnosed with metastatic disease of bone is the initiation of androgen deprivation therapy (ADT). By robbing the cancer of its growth factor, testosterone, one can reliably delay the progression of the cancer for what is typically several years. However, the concomitant effects of ADT on bone density and general skeletal health can compound the risk of SREs in men with metastatic tumor in bone.

Because prostate cancer is the most common malignancy diagnosed in men, it serves as one of the model systems to study how bone metastases influence survival, therapeutic decision making, and quality of life. This chapter does not attempt to reiterate the general management of bone tumors explained elsewhere in the book. It focuses on the elements that are specific to prostate cancer, with an emphasis on adenocarcinoma, which accounts for over 95 % of diagnoses.

J.D. Tward, MD, PhD (✉)
Radiation Oncology, Huntsman Cancer Hospital, University of Utah, 1950 Circle of Hope Drive, Salt Lake City, UT 84112, USA
e-mail: jonathan.tward@hci.utah.edu

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Biological Aspects Particular to Prostate Bone Metastases

Blastic Appearance

Prostate cancer bone metastases usually appear on X-rays as dense structures, suggesting osteoblastic reactions around tumor. Nevertheless, studies have also demonstrated that prostate bone metastases also have osteolytic properties, which in turn weaken and destroy the bone and are the presumed cause of the morbidity related to fractures [4].

Histologies

Adenocarcinoma accounts for 95 % of all prostate cancer diagnoses. Rarer histologies include sarcoma, mucinous or signet-ring cell carcinomas, adenoid cystic carcinomas, carcinoid tumors, large prostatic duct carcinomas (including the endometriod-type adenocarcinomas), melanomas, and small-cell undifferentiated cancers. Amongst these rarer histologies small-cell cancer may be the next most prevalent diagnosis at around 1 % of subjects. Unlike the adenocarcinomas, the neuroendocrine variants have a high incidence of bone metastases which are predominantly lytic.

Demographics and Prognosis of Men with Metastatic Prostate Cancer

Prostate cancer accounts for the majority of bone metastases diagnosed in men in the USA [5]. In a contemporary study utilizing the large SEER-MEDICARE claims database, 7.7 % of men with prostate cancer had evidence of bone metastasis at diagnosis. These men were more likely to be older than a matched cohort of men without bone metastasis (median age of 76 versus 74). Race and comorbidity do not appear to influence the risk of presenting with bone metastasis at diagnosis, and the hazard ratio of death is 6.6-fold for those with bone metastasis and no evidence of SREs at presentation compared to those without bone metastases [6]. When both bone metastasis and SREs are present at diagnosis, the hazard ratio for death climbs to 10.2.

Detection of Bone Metastasis

Occult Disease and Proposed Mechanism of Spread

Clinically occult prostate cancer bone metastases are discovered in a relatively large proportion of men with either known or unknown primary cancers at the time of autopsy. In a Swiss autopsy series of over 19,000 men who died of various causes between 1965 and 1995 (most prior to the era of PSA-screen detection), macroscopic localized prostate cancer was detected in 8.2 % of subjects [7]. Roughly half of these men had been diagnosed with prostate cancer during their lifetimes. Bone metastasis was identified in about 30 % of these men. The spine had bone metastasis in 90 % of the cases. In men with spinal disease, the lumbar vertebra were involved 97 % of the time, followed by thoracic spine at 66 %, and cervical spine at 38 %. Isolated metastases to the thoracic and cervical spine only occurred in 2 % and 1 % of men, respectively. Other bony sites outside the spine were not meticulously examined in this particular autopsy series.

The presence of bone metastasis in this autopsy series was strongly correlated with the presence of lymphatic metastasis. Bone metastases were identified in approximately 80 % of persons with lymphatic metastasis, but in only about 16 % of persons without evidence of lymphogenous spread. Para-aortic lymph node metastases were identified in ~58 % of persons with spine metastasis, but in only about 39 % of those without spinal metastasis. Taking these distributions into account, the authors propose that the route of bone metastases for prostate cancer follows two pathways: the first supporting the concept first proposed by Batson via a “backward spread” of metastasis from the prostatic veins into the lower lumbar spine followed by subsequent upward spread along spinal veins, and the second pathway via the usual hematogenous route of circulating tumor cells pumped through the lungs on their way to other bony sites [8].

Clinical Detection of Bone Metastasis

A clinical risk grouping system first proposed by D'Amico and then adopted and modified by the NCCN is typically used to determine who should be screened for prostate bone metastasis in men without symptoms of bony disease. Most treatment guidelines, such as those of the NCCN, recommend obtaining scans in men with "high-risk" prostate cancers, defined as men with a biopsy Gleason score of 8–10, a clinical T-stage of T3 or greater, or a PSA exceeding 20. For those with "low-risk" cancers (Gleason score <7, PSA < 10, no significant palpable disease on digital rectal exam), screening for bone metastasis is not indicated due to the low likelihood of detecting bone metastasis [9, 10]. The guidelines vary slightly from one another on criteria for obtaining scans in intermediate-risk patients and are summarized in Table 5.1.

The most common diagnostic test used to screen for bone metastases in newly diagnosed prostate cancer patients is the technetium bone scan (Fig. 5.1). Numerous studies evaluating how PSA values correlate with the likelihood of detecting bone metastasis have been performed. In men with serum PSA values of at least 10 ng/dl, Tc bone scan has reportedly detected bone metastasis in between 0.6 and 45.8 % of subjects. However, in studies evaluating a cutoff of 20 ng/ml, the detection range is reported to be between 14 and 26.5 % of persons [9].

In a contemporary series of over 800 newly diagnosed prostate cancer patients with Gleason 8–10 (high-risk) cancers, bone metastases were detected in 17 % of men. In men with palpable disease on digital rectal examination having lower Gleason scores, bone metastasis was discovered in 8 % of men [9].

In men with androgen-insensitive prostate care without evidence of bone metastases (i.e., those with rising PSA values despite the use of therapies designed to remove or block testosterone

Table 5.1 Summary of guidelines for staging imaging studies in men with prostate cancer

Guideline	Recommendation for bone scan	Recommendation for CT/MRI
National Comprehensive Cancer Network (NCCN) [10]	Symptomatic patients Those with a life expectancy >5 years and … PSA >20 T2 disease with PSA >10 T3–T4 disease Gleason score 8–10	T3–T4 T1–T2 and nomogram-predicted probability of lymph node metastasis >10 %
European Association of Urology (EAU) [11]	Bone pain Poorly differentiated tumors and locally advanced disease irrespective of the serum PSA level	
American Urology Association (AUA) [12]	PSA >20	PSA >20 Locally advanced disease Gleason 8–10
European Society for Medical Oncology (ESMO) [13]	T3–T4 Gleason score 8–10 PSA > 20 Intermediate risk and … Clinical suspicion of bone metastases Gleason 4 + 3 PSA greater than 10	Consider in high-risk patients
European Society of Urogenital Radiology (ESUR) [14]	High-risk patients	Active surveillance patients Intermediate-risk patients to plan curative intent therapy approaches High-risk patients

Adapted and modified from Briganti et al. [2]

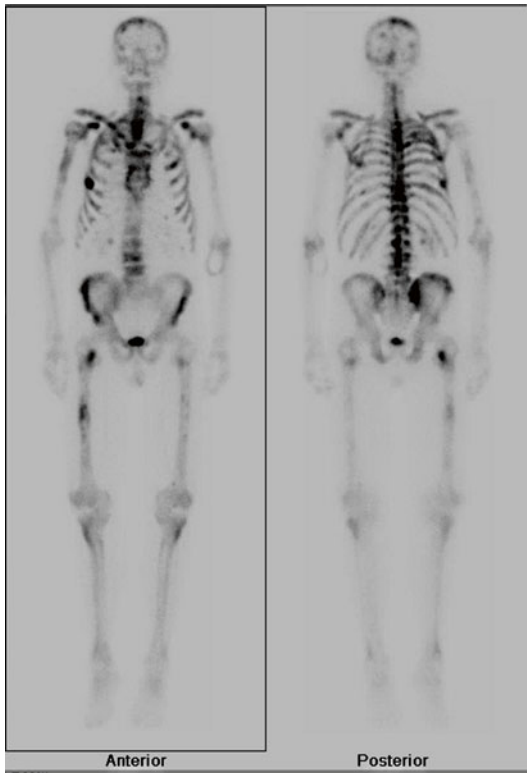

Fig. 5.1 Technetium bone scan: Numerous bone lesions throughout the axial and appendicular skeleton in a man with metastatic prostate cancer are shown. Note the heavy involvement of the spine, which is typical

to castrate levels in the serum), bone metastases developed by 2 years in approximately 40 % of subjects [2, 15, 16]. In subgroup analyses of a randomized trial in patients who had androgen-insensitive prostate cancer, a baseline PSA level of >24 ng/dl or a PSA doubling time of less than 6 months was correlated with the highest risk of developing bone metastases, with a reported rate exceeding 70 % by 3 years [2, 16].

Therapy

Prevention of Bone Metastases

Role of Surgical Treatment of the Primary Cancer

Approximately 85 % of men with newly diagnosed prostate cancer have disease clinically localized to the prostate alone. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) trial [17], which studied a mostly PSA-screened population randomized to radical prostatectomy or observation, reported on some nonmortality endpoints. They found an absolute risk reduction of 6 % in the prostatectomy group over the watch-and-wait group (number needed to treat of 17) to prevent bone metastasis. Notably, this change in development of bone metastases was realized almost exclusively within the first 8 years following diagnosis and treatment.

Role of Androgen Deprivation Therapy Plus or Minus Radiation Therapy

There have been three randomized trials completed comparing the efficacy of the addition or radiotherapy to androgen deprivation therapy alone in men with high-risk but clinically localized prostate cancer. All of the studies showed a significant disease-specific and overall survival benefit by the addition of radiation to the primary site [18–20]. One of the trials specifically reported on metastasis-free survival, which implies a delay in the development of bone metastases specifically. After 8 years of follow-up, 11 % of subjects on androgen deprivation alone (continuous leuprolide with flutamide) developed bone metastases, as opposed to only 3 % of those persons who had combined ADT and radiotherapy [18].

Treatment of Bone Metastases

Role of Bisphosphonates

There have been numerous randomized trials evaluating the efficacy of bisphosphonates versus placebo in the treatment of bone metastases for various malignancies. The majority of the studies included subjects with any histologies, most commonly those with breast prostate multiple myeloma and lung cancer [21]. There are several randomized trials that have restricted their subjects to those with prostate cancer [22–25]. The Cochrane Collaboration has performed a systematic review of these randomized trials as it pertains to pain relief. When restricting the analysis to prostate-only studies, and pain relief at 12 weeks as the endpoint, the Cochrane group reported an odds ratio of 1.81 favoring bisphosphonate

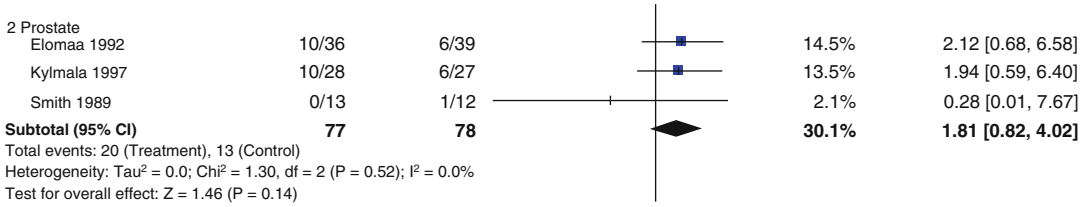

Fig. 5.2 Meta-analysis of bisphosphonates on alleviating prostate cancer bone pain. From Wong, R. and P.J. Wiffen, Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database Syst Rev, 2002(2): p. CD002068. Reprinted with permission from John Wiley and Sons

treatment over control. The 95 % confidence interval ranged from 0.82 to 4.02 (Fig. 5.2). Technically, this can be interpreted as not reaching "statistical significance." The conclusion of the reviewers as it specifically pertained to primary disease sites was that "The small numbers of studies meant conclusions could not be made regarding the relative effectiveness of bisphosphonates on patients with different primary disease sites." Overall, however, in pooled analyses of all disease sites, the number needed to treat to achieve pain relief with bisphosphonates at 4 weeks was 11 and at 12 weeks 7 [21]. A more detailed overview of bisphosphonates in the treatment of bone metastases will be addressed elsewhere in this book.

Role of External Beam Radiation Therapy

Randomized trials of treatment with conventional radiotherapy have shown complete pain relief rates ranging from 15 to 54 %, and partial pain relief rates ranging from 28 to 89 % for persons with bone metastases [26–38]. These trials did not restrict subjects to those with prostate cancer, although breast and prostate patients accounted for the majority of subjects. The Bone Pain Trial Working Party Group showed a median time to pain relief in all patients of approximately 1 month, and a median time to complete pain response of 3–4 months, whereas median time to first increase in pain was approximately 12 months or longer [26]. Stereotactic body radiotherapy (SBRT) is an emerging treatment modality delivering five or fewer highly conformal, high-dose radiation treatments to bone metastases. Early outcomes claim superior pain relief and control over conventionally fractionated radiations, but randomized trials are currently ongoing. A complete overview of radiotherapy as it applies to the treatment and efficacy of bone metastases is discussed in the chapter on radiotherapy elsewhere in this book.

Role of Parenteral Radionuclides

Radionuclides can be used in patients with widespread prostate cancer bone metastases where focal therapies such as surgery or radiation will not be expected to palliate the symptoms. Radionuclide therapy is generally aimed at persons with osteoblastic or mixed-type lesions, as the mechanisms of action are particularly targeted to blastic/sclerotic processes. The isotopes currently in use are strontium-89, samarium-153, and more recently radium-223. Both radium and strontium are in the same column of the periodic table of the elements as calcium, and therefore act as calcium mimetics. They emit beta-particles which exert their tumoricidal properties. As such, they intercalate into bone where calcium would otherwise be deposited and effectively act as very targeted radiotherapies. Likewise, samarium-153 is a chelated tetraphosphonian compound that selectively accumulates in places of bone transformation by binding to hydroxyapatite.

Strontium-89 and Samarium-153

Two systematic reviews evaluating the role of strontium or samarium for the palliation of painful bone metastases have been completed [39, 40]. In the most complete and contemporary review by the Cochrane Collaboration, the conclusion

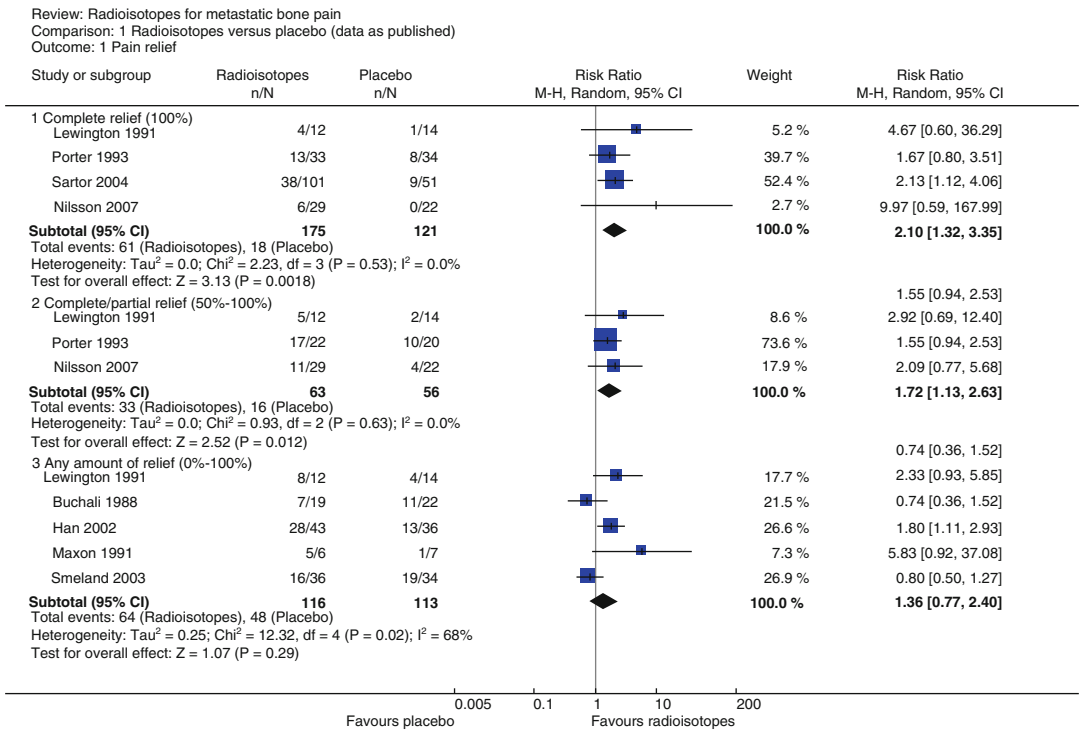

Fig. 5.3 Beta-emitting radionuclides for bone pain meta-analysis. From Roque, I.F.M., et al., Radioisotopes for metastatic bone pain. Cochrane Database Syst Rev, 2011(7): p. Cd003347. Reprinted with permission from John Wiley and Sons

was that there was a "small benefit" of these isotopes in providing "complete" or "complete/partial" pain relief over 1–6 months (NNT = 5 and 4, respectively). Nevertheless, the review also reported that there was "no conclusive evidence to demonstrate that radioisotopes modify the use of analgesia with respect to placebo" (hazard ratio 1.36 favoring isotopes, 95 % CI 0.77–2.40) (Fig. 5.3). Furthermore, radioisotopes did not reduce the risk of spinal cord compression (HR = 1.10, 95 % CI 0.39–3.07) [40]. Neither strontium nor samarium treatment has been shown to impact overall survival.

Radium-223

Recently, radium-223 has been FDA approved for the treatment of prostate cancer bone metastases in men with castration-resistant disease. Radium-223 is an alpha particle emitter, which means that it will selectively destroy cells within only a few cell diameters (less than 100 μm) of where it is intercalated into bone as a calcium mimetic. This short path of the alpha particles results in a minimization of toxic effects to the bone marrow and adjacent healthy tissues. The landmark ALSYMPCA trial (Alpharadin in Symptomatic Prostate Cancer Patients) is a phase 3, randomized, double-bind, placebo-controlled trial with mature results [41]. Unlike other parenteral radioisotopes, the use of radium-223 showed a significant overall survival benefit in men with castration resistant prostate cancer (HR = 0.7, 95 % CI 0.58–0.83; median survival 14.9 months versus 11.3 for placebo). Secondary endpoints of the study all significantly favored radium-223 including time to first symptomatic skeletal event (HR 0.66, 95 % CI 0.52–0.83—median time 15.6 months versus 9.8 months placebo); and time to increase in PSA level (HR 0.64, 95 % CI 0.54–0.77—median time 3.6 months versus 3.4 months

placebo). Most notably, there were *fewer* adverse events in the radium-223 cohort than the placebo group. Given the overall survival benefit, decrease in SREs, and low side effect profile of radium-223, there is much excitement within the oncologic community about using this therapy in combination with other therapies such as chemotherapy, newer generation androgen deprivation therapy agents, and focal radiotherapies in men with metastatic prostate cancer.

Role of Androgen Deprivation Therapy

The 1966 Nobel Prize for Physiology or Medicine was awarded to Charles Huggins for the discovery that androgen ablation therapy causes regression of primary and metastatic prostate cancer [42]. The production of serum testosterone is primarily controlled by the hypothalamus via its production of luteinizing hormone-releasing hormone (LHRH) which acts on the anterior pituitary gland to release luteinizing hormone (LH). Within the testicle the LH is recognized by the Leydig cells within the testes signaling the production of testosterone. This pathway accounts for about 90 % of the production of serum testosterone. The remaining 10 % is peripherally produced by adrenal steroid conversion into testosterone (Fig. 5.4). Numerous drugs have been developed that target various points along these pathways, which ultimately interfere with testosterone signaling within the cancer cell. These include LHRH agonists (leuprolide, goserelin, triptorelin), LHRH antagonists (degarelix acetate), nonsteroidal antiandrogens that bind the androgen receptor (bicalutamide, flutamide, enzalutamide), and 17 α-hydroxylase/C17,20 lyase inhibitors (abiraterone). In men with metastatic disease, initial androgen deprivation therapy results in a median progression-free survival of 12–33 months [43, 44]. However, one can use the serum PSA value after initiation of ADT to prognosticate life expectancy. The Southwest Oncology Group (SWOG) performed a randomized trial evaluating the effect of immediate and continuous androgen deprivation therapy versus intermittent androgen deprivation for men with metastatic prostate cancer. All men in this trial had 7 months of induction ADT. The median survival was 13 months for patients with a PSA of more than 4 ng/ml after induction therapy, 44 months for patients with a PSA of more than 0.2–4 ng/ml or less, and 75 months for patients with PSA of 0.2 ng/ml or less [45]. In subjects with bone pain enrolled on the trial, there was a trend towards improved overall survival for continuous androgen deprivation therapy, but overall the results of for non-inferiority of intermittent versus continuous ADT were inconclusive for the trial [46].

Role of Surgical Therapy

Surgery for prostate cancer bone metastases is indicated to prevent or stabilize pathologic fractures, decompress spinal cord or nerve root compression, and palliate pain if other modalities fail to do so. The details of surgical management and indications will be addressed elsewhere in this textbook.

Role of Chemotherapy for Bone Metastasis

Chemotherapy for metastatic prostate cancer is generally reserved for the treatment of prostate cancer in symptomatic men who are no longer responding to therapies directed at disruption of androgen signaling (sometimes referred to as "castration resistant" or "androgen insensitive"). Contemporary agents routinely used include mitoxantrone, docetaxel, and cabazitaxel. One randomized trial assessed pain response in men with androgen-insensitive prostate cancer randomized to mitoxantrone plus prednisone versus prednisone alone. Those receiving mitoxantrone had a better palliative response (29 % versus 12 %), and the duration of palliation was longer in the chemotherapy group (43 weeks versus 18) [47]. In another randomized trial, mitoxantrone was randomized against cabazitaxel and although cabazitaxel did have a survival advantage over mitoxantrone, the palliation benefits were similar between the two drugs [48].

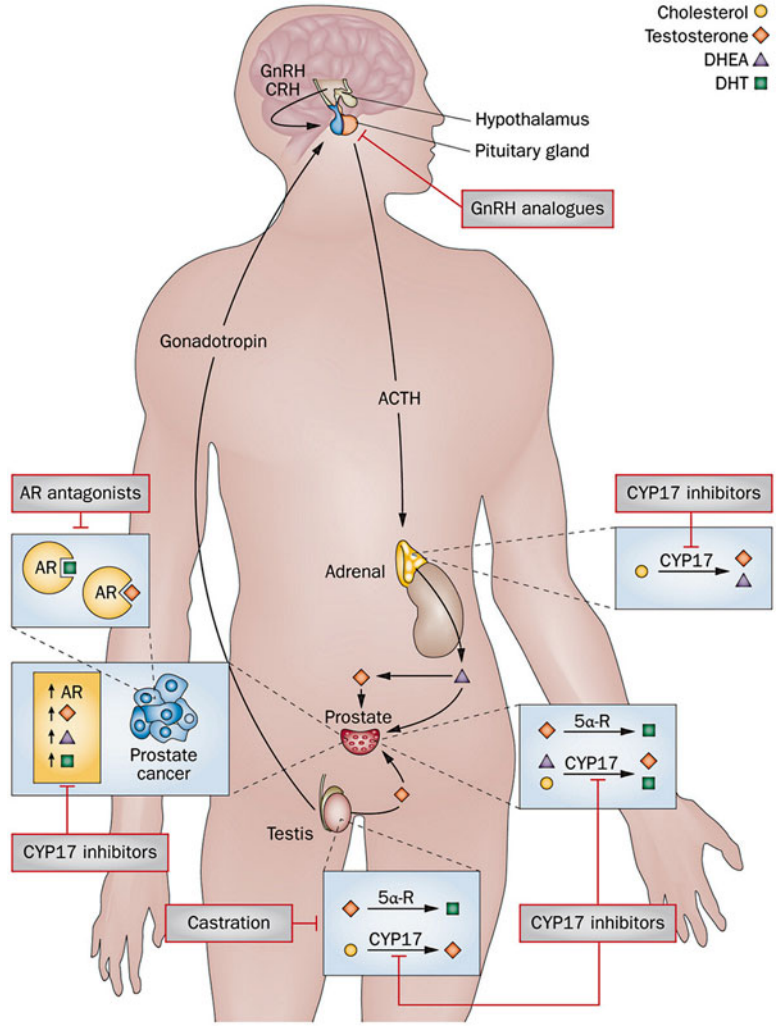

Fig. 5.4 The androgen axis and its targets. From Yin L, Hu Q. CYP17 inhibitors—abiraterone, C17,20-lyase inhibitors and multi-targeting agents. Nat Rev Urol. 2014 Jan;11(1):32–42. Reprinted by permission from Macmillan Publishers Ltd. Copyright 2014

Conclusion

Because prostate cancer bone metastases are common, much is known about its prognosis and treatment. Because the disease is sensitive to hormone manipulation, radiation, chemotherapeutic, and surgical therapies, it serves as an excellent model system for research. It is one of the only cancers where treatment of the bone metastases specifically has resulted in a survival benefit for the patients [41]. Ongoing prospective studies are investigating whether treatment of oligometastatic bone-only disease will result in potential cure or survival benefit. Furthermore, interventional ablative therapies are also emerging as a possible treatment of prostate bone metastases. Because skeletal-related events (SREs) are an important source of morbidity and decreased quality of life for prostate cancer patients, frequent surveillance and treatments to prevent progression of metastatic bone disease are the care standard.

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