



## Review - Prostate Cancer

# Natural History and Treatment of Bone Complications in Prostate Cancer

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### Abstract

Bone metastases are highly prevalent in patients with prostate cancer, and they commonly present a therapeutic challenge. The natural history of prostatic bone metastases is characterized by skeletal morbidity, often producing distressing symptoms for individual patients and reducing patient autonomy and mobility. These bone metastases are usually radiologically osteoblastic, but there is also a strong osteolytic component as evidenced by marked increases in bone resorption markers. Malignant bone lesions can reduce the structural integrity of the skeleton, resulting in skeletal complications such as pathologic fracture, spinal cord compression, and severe bone pain, which adversely affect quality of life.

Preclinical and clinical studies have provided insight into the pathophysiology of malignant bone disease from prostate cancer and suggest that bone-directed therapies, including radionuclides, endothelin-1 antagonists, and bisphosphonates, may provide both palliative and therapeutic benefits. Clinical investigations with these agents are underway in patients with prostate cancer to gain insight into the pathophysiology of bone metastases and to evaluate the role of bone-specific therapies in treating and preventing bone metastases.

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## 1. Introduction

Prostate cancer is the most common genitourinary tract malignancy; its prevalence is especially high in North America and Western Europe [1], where

greater accessibility to healthcare and implementation of methods for the early diagnosis of prostate cancer may contribute to a higher reported incidence. In these regions, the long-term survival statistics for prostate cancer are favorable. However,

treatment is rarely curative once the cancer has spread beyond the prostate. In these patients, the long-term effects of cancer and its treatment by androgen deprivation therapies (ADT) contribute to an ongoing risk for skeletal morbidity and a concomitant decrease in quality of life [2].

Prostate cancer metastasizes to bone in approximately 65% to 75% of men with advanced disease [3], and the number of bone lesions is predictive of limited response to ADT and poor survival [4]. Bone metastases produce local disruptions of the skeletal architecture with replacement of the normal skeleton by abnormal bone. At the same time, bone resorption from the tumor-free skeleton is also increased, leading to an accelerated rate of bone loss in skeletal areas that are free from metastases [5,6]. This predisposition to osteopenia may be worsened by decreases in bone volume and bone mineral density as a result of ADT [7,8]. Bone metastases may be associated with severe bone pain and the development of potentially debilitating skeletal complications such as pathologic fracture and spinal cord compression. Median survival after diagnosis of such metastasis is approximately 2 to 3 years [9], depending on the hormone responsiveness of the disease. Therefore, patients with advanced prostate cancer may survive for a prolonged time with a risk of developing skeletal

complications. Patients can also experience multiple skeletal complications from the time of diagnosis to death. The mechanisms by which bone metastases develop and their underlying pathophysiology have been extensively investigated [10-12], and effective therapies for bone lesions in patients with prostate cancer are emerging [13,14]. Successful management of skeletal health may result in better maintenance of quality of life throughout the continuum of care for men with prostate cancer.

## 2. Prostate cancer metastasis to bone

Prostate cancer metastasizes to bone more frequently than does any other solid tumor [3]. Bone metastasis occurs in almost all patients during the natural course of their disease and typically targets the lumbar spine, vertebrae, and pelvis [15]. There are many causes for this high incidence of bone metastasis, including anatomic factors facilitating accessibility of the lumbar spine, innate characteristics of prostate cancer cells, and molecular interactions between prostate cancer cells and the bone microenvironment. Indeed, prostate cancer seems uniquely suited to growth in bone [16,17].

Metastasis to bone via the circulatory or lymphatic system is a multistep process (Fig. 1) [10]. Prostate

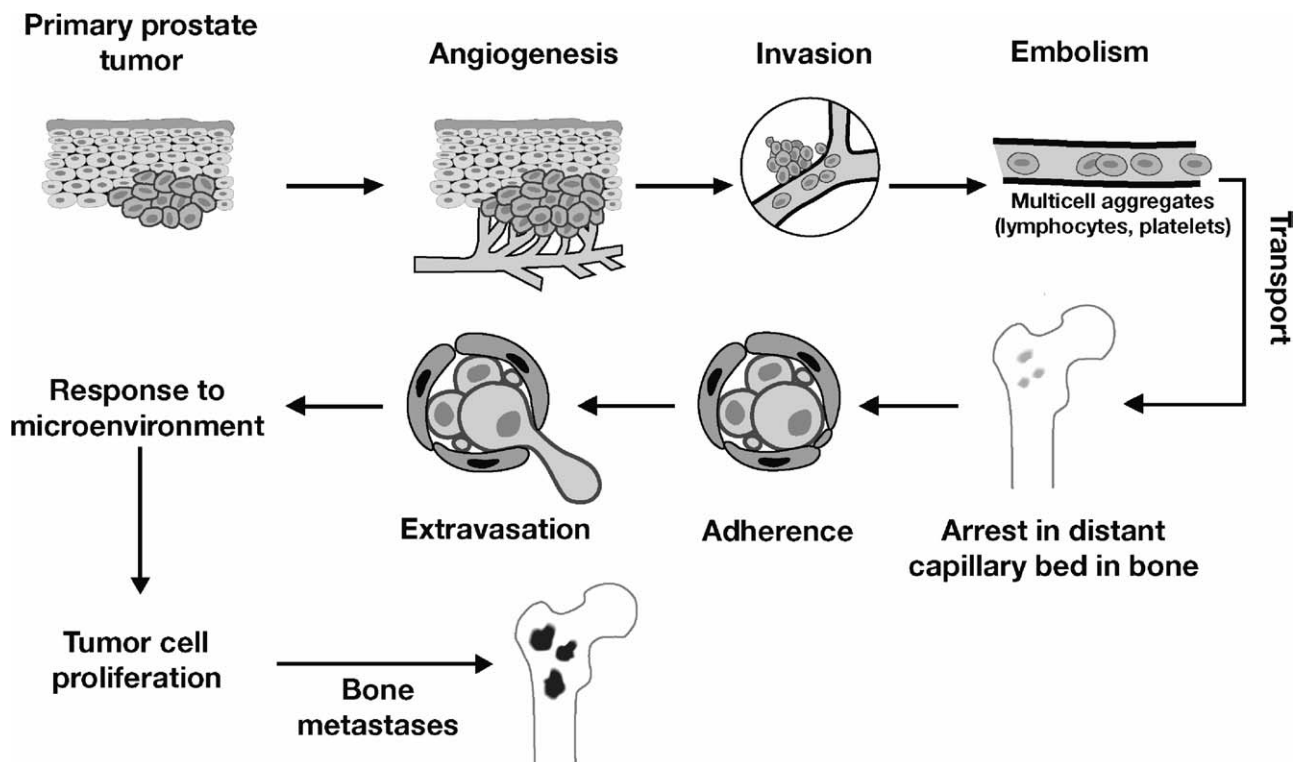


Fig. 1 – General mechanism of tumor cell metastasis to bone. Multiple steps are required for prostate cancer to metastasize to bone. Adapted with permission from Guise and Mundy [10].

cancer cells characteristically spread to the vertebrae via Batson's plexus. Prostate epithelial cells also circulate freely in the blood of men with advanced prostate cancer [18–21].

### 2.1. Early steps in metastases to bone

Metastasizing cells arrest in the bone marrow endothelium, where they are immobilized in capillary beds. Tumor cell binding is a rapid and highly selective process, with tumor cells binding to specific endothelial cells at preferred metastatic sites and actively migrating through gap junctions [16,17,22]. This process of extravasation is complete within 24 h *in vitro* [23]. Cytokines, which are often embedded within bone matrices, may be chemoattractants for prostate cancer cells [24]. Bone-derived factors such as bone morphogenetic protein 4 (BMP-4) increase the adhesion of prostate cancer cells to bone marrow endothelium [12]. Animal models suggest that bone matrix factors such as stromal cell-derived factor 1 enhance the migration of prostate cancer cells across the endothelial boundary [11]. Adherence and extravasation may also be facilitated by the protease-activated receptor 1 (PAR1), also known as the thrombin receptor, which is expressed at very high levels in human prostate cancer cell lines [12]. Activation of PAR1 promotes cell adhesion to extracellular matrix proteins, cell motility and migration, and secretion of matrix metalloproteinases (MMPs). Matrix metalloproteinases are important for breaking down basement membranes and facilitating metastatic spread [10,25–27].

It has also been hypothesized that growth factors released during osteolysis can stimulate the growth not only of osteoblasts but of tumor cells that metastasize to bone. Indeed, preclinical evidence suggests that bone resorption (osteoclast-mediated osteolysis) may be a crucial element in the development of bone metastases [10,28–30]. However, this evidence, although compelling, has not been validated in human bone metastases.

### 2.2. Formation of bone lesions

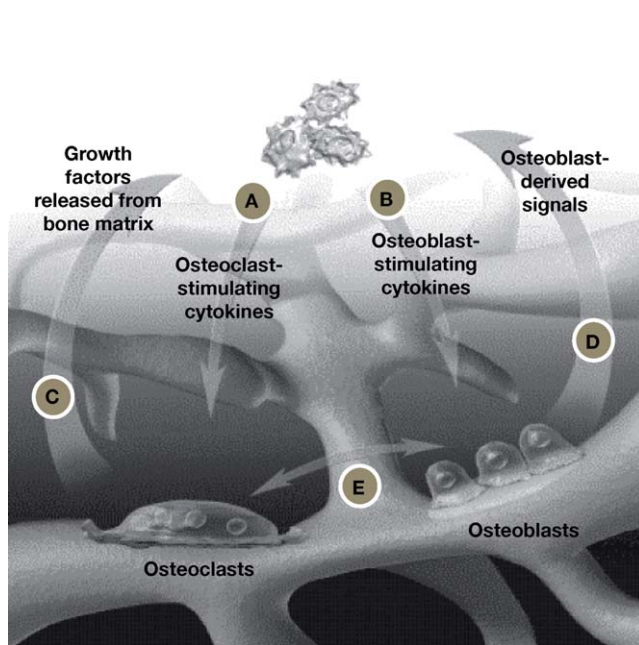
Once established within the bone microenvironment, prostate cancer cells and the cells that maintain skeletal homeostasis participate in a complex interplay that results in perturbations of bone metabolism and increases in tumor growth. During osteolysis, growth factors contained in the bone matrix, predominantly transforming growth factor-beta (TGF- $\beta$ ) and insulinlike growth factor 2 (IGF2), are released, causing paracrine stimulation of osteoblasts to repair the bone at the site where

osteolysis occurred. This coupled activity preserves the structural integrity of the skeleton and contributes to serum ion homeostasis [10,13].

The pro-osteogenic effects of prostate cancer tumors are mediated through complex interactions between tumor and bone. Metastatic prostate cancer cells secrete TGF- $\beta$  and endothelin-1 (ET-1), which exert localized effects on bone metabolism (Fig. 2) [14,31–35]. Prostate cancer cell lines also secrete BMPs, parathyroid-related hormone [36,37], prostate-specific antigen (PSA), IGFs [35,38,39], and an amino-terminal fragment of the protease urokinase, which has mitogenic effects on osteoblasts [31]. BMP-6 expression is relatively high in primary prostate cancer tumors and in established skeletal metastases from prostate cancer. However, BMP-6 expression is weaker in skeletal metastases from other tumors, suggesting that BMP-6 expression might be one factor that predisposes prostate cancer cells to metastasize to bone [40]. Additionally, BMPs and the other growth factors may cause a shift in local bone homeostasis toward a characteristic osteoblastic phenotype. This may be achieved through the interaction with prostate-secreted kallikrein 2 and PSA [16]. Prostate-specific antigen may also be more directly involved in the predominantly osteoblastic phenotype [41]. Parathyroid-hormone-related protein, which stimulates bone resorption, may be cleaved by PSA, resulting in decreased bone resorption. Additionally, PSA hydrolyzes IGF-binding proteins, allowing IGF1 to stimulate osteoblast proliferation. Endothelins involved are synthesized in vascular endothelial cells, and their functions include vasoconstriction, nociception, and the physiologic regulation of bone function. Studies have shown that exogenous ET-1 induces prostate cancer proliferation and enhances the mitogenic effects of IGF and epidermal growth factor [42]. More importantly, in relation to prostate cancer metastasis in bone, ET-1 production is one of the major factors responsible for osteoblast overstimulation [43]. Prostate epithelial cells produce ET-1 and, furthermore, produce ET-1 in a bone environment as prostate cancer cells [44]. In fact, the effect of ET-1 in prostate cancer has provided a new treatment target; a recent randomized, placebo-controlled trial demonstrated that an ET<sub>A</sub> antagonist suppressed markers of bone metabolism in patients with hormone refractory prostate cancer [14,45].

## 3. Clinical consequences of bone metastases

In patients with prostate cancer, metastasis to bone is often accompanied by the onset of severe bone



**Fig. 2 – Pathophysiology of osteolytic/osteoblastic metastatic bone disease in prostate cancer. (A)** Metastatic tumor cells release humoral factors (osteoclast precursors such as parathyroid hormone-related protein, interleukin-6) that stimulate osteoclastic recruitment and differentiation. **(B)** Prostate cancer cells concomitantly produce soluble paracrine factors (transforming growth factor beta, insulin growth factor, bone morphogenetic protein), causing excessive osteoblast activation. **(C)** osteoclastic (osteolytic) activity releases growth factors (transforming growth factor beta) that stimulate tumor-cell growth, perpetuating a vicious cycle of excessive bone resorption. **(D)** Osteoblastic activation in turn releases unidentified osteoblastic growth factors that also stimulate tumor-cell growth, contributing to the perpetual cycle of abnormal bone formation. **(E)** Additionally, the normal interplay between osteoclast and osteoblast activity is perturbed. The imbalance in activities can cause compensatory bone loss at skeletal sites distant from the sites of metastasis. Reprinted with permission from Saad and Schulman [35].

pain and other complications, including pathologic fracture and spinal cord compression, similar to patients with predominantly osteolytic bone lesions [46]. Indeed, bone metastases from prostate cancer are generally highly symptomatic and contribute to an ongoing erosion in quality of life for patients with advanced cancer [47]. Malignant bone lesions are classified by their radiologic appearance as osteolytic, osteoblastic, or mixed (Fig. 2). Bone lesions from prostate cancer are characterized by osteoblastic overactivity, exhibiting localized increases in osteogenesis [48]. In osteoblastic lesions, prostate cancer cells stimulate the maturation and activation of

osteoblasts [49]. Osteoblasts, in turn, appear to stimulate prostate cancer growth and reduce proapoptotic signaling [50,51].

Although osteoblastic lesions are associated with pathologic new bone formation, this does not correlate with increases in bone strength. On the contrary, the new osseous tissue is often abnormally mineralized or inappropriately placed [5,10,52]. Furthermore, osteoblastic bone metastases can trigger localized increases in osteolysis to balance the excess activity of osteoblasts [31–34,48,53]. Excess osteogenesis can also cause systemic increases in osteolysis, resulting in generalized osteolysis at distant sites. The overall result is uncoupling of the osteogenesis and osteolysis processes. In most cases, disease progression in patients with bone metastases from prostate cancer is associated with mild hyperparathyroidism [54], perhaps from decreases in serum calcium levels caused by new bone formation. This “bone hunger syndrome” is associated with serum ion perturbations and systemic increases in osteolysis and progressive bone loss in the tumor-free skeleton [5,6,55].

The effects of bone metastases secondary to hormone-refractory prostate cancer are illustrated by the placebo-control arm of a recent randomized clinical trial of zoledronic acid [56,57]. Although all patients in this trial were receiving standard therapy for their primary cancer, 49% of patients experienced at least 1 skeletal complication over 2 years of follow-up, and these events occurred at an average rate of 1.5 skeletal complications per patient per year (patients who experienced skeletal complications had a mean incidence of approximately 3 events per year) [56]. The incidence of each type of skeletal complication is summarized in Table 1 [56,57]. Approximately one-third of the patients required palliative radiotherapy for bone pain, and

**Table 1 – Proportion of patients with bone metastases from hormone-refractory prostate cancer who experienced skeletal complications while on study (n = 208)**

Skeletal complication	Proportion of patients, %
Any event	49
Radiation to bone	33
Pathologic fracture	25
Spinal cord compression	8
Change in antineoplastic therapy to treat bone pain	7
Surgery to bone	4
Hypercalcemia of malignancy	1

Data are from the placebo-control arm of a phase III clinical trial of zoledronic acid [56,57].

one-quarter of the patients experienced at least 1 pathologic fracture.

A recent retrospective review of clinical records of men with prostate cancer treated during a 4-year period ( $N = 634$ ) revealed further insight into the burden of disease from bone metastases [58]. Of 119 patients with vertebral metastases (the most common site for solitary metastases in patients with prostate cancer) [15], 111 (93%) reported pain and 30 (25%) developed motor impairment [58]. Fifteen patients required surgery for spinal cord compression. Additionally, hormone therapy (163 episodes), chemotherapy (70 episodes), and radiation therapy (103 episodes) were required to treat bone lesions. Treatment reduced pain in 77% of episodes and improved motor function in 50% of episodes, but problems tended to recur (average of 1.78 events per patient; range, 1 to 8). Patients survived a median of 14 months after vertebral metastases were diagnosed. However, despite state-of-the-art care for their disease, patients experienced pain and neurologic complications that strongly affected their quality of life.

Skeletal complications have been shown to significantly reduce health-related quality of life in patients with prostate cancer [59]. A Functional Assessment of Cancer Therapy–General (FACT-G) analysis of 248 patients who experienced skeletal complications during a recent 2-year clinical trial revealed significant decreases in Physical Subscale scores after any skeletal complication, in Functional Subscale scores after any skeletal complication other than pathologic fracture, and in Emotional Subscale scores following palliative radiation therapy or pathologic fracture [59]. Significant reductions in FACT-G occurred after palliative radiation therapy. In addition, patients who experienced their first skeletal complication during the study showed an increase in the Social/Family Subscale score [59], suggesting that these events affect many aspects of a patient's support network and may increase demands on caregivers.

Skeletal complications from prostate cancer may have severe long-term effects. Pathologic fractures can have especially grim implications because the majority require radiotherapy and/or orthopedic surgery. Additionally, extensive rehabilitation is required to restore function when weight-bearing bones are involved [60]. Surgery for pathologic fracture is associated with a 4% postoperative fatality rate [61]. Furthermore, surgery fails to restore mobility in approximately 25% of patients with pathologic fractures of the long bones of the leg [62]. Hip fractures in men are associated with a particularly poor prognosis. Poor et al. [63] assessed

clinical spectrum, treatment, and short-term outcomes in men who contracted hip fractures after moderate trauma. In their study of 131 elderly men with hip fractures, 16% died within 30 days after their fractures, and roughly 60% of those who did survive failed to regain their mobility [63].

There is a consistent correlation of skeletal disease burden with bone metabolism and survival [64] and skeletal fractures and survival in patients with prostate cancer [65]. In a review of 195 consecutive patients receiving long-term ADT for prostate cancer, overall survival was significantly lower for patients who experienced a fracture during the course of their disease compared with those who did not (median survival, 121 months versus 160 months, respectively;  $p = .04$ ) [65]. In addition to their effects on prognosis, skeletal complications increase treatment costs [66], placing a greater burden on healthcare resources.

#### 4. Effects of ADT on the skeleton

Chemotherapy and hormone therapy are associated with bone loss in cancer patients [67]. Cancer treatment-induced bone loss (CTIBL) is especially prevalent in men who are undergoing ADT for prostate cancer. The severity of bone mineral density (BMD) decreases from CTIBL exceeds that of benign bone loss associated with aging and menopause [8,68], placing patients at risk for fractures. Recent guidelines and treatment recommendations for CTIBL reflect the increased awareness of this condition within the oncology community [69].

Several studies have investigated the effects of ADT on bone loss in men with prostate cancer. Eriksson et al. [70] examined the effects of orchiectomy in men with prostate cancer and found that, 1 year after surgery, BMD was reduced by 9.6% in the hip and 4.5% in the radius in these patients. Daniell et al. [71] also analyzed BMD in the femoral neck bone in patients who had been orchiectomized. They demonstrated that BMD decreased by 2.4% and 7.6% during years 1 and 2, respectively. Several studies have evaluated the effects of luteinizing hormone-releasing hormone (LHRH) agonists and gonadotropin-releasing hormone agonists on BMD [71–73]. Each of these studies showed significant reductions in BMD during ADT. Patients with prostate cancer without bone metastases treated with intermittent androgen suppression have also experienced a significant reduction in BMD, as shown in a study by Higano et al. [74]. Among patients with normal BMD at baseline, the mean BMD had decreased by 4.5% at the lumbar spine and

2.5% at the hip after 9 months of ADT. During the off-treatment period (median 7.9 months), the mean changes in BMD relative to the post-ADT values were 1.5% for lumbar spine and -0.01% for hip. Interruption of ADT attenuated the rate of bone loss; however, recovery to baseline BMD values was not achieved in all patients. Together, the results of these studies suggest that ADT reduces BMD and that this may increase the risk of skeletal fractures in men with prostate cancer. In fact, new evidence indicates that ADT increases the risk of bone complications to a greater extent than was previously thought; Krupski et al. [75] showed that fracture rates were increased by 16% to 42%.

Antiandrogen therapy, which blocks the androgens locally in the prostate, is indicated in the United States for use in combination with an LHRH agonist. Although data are sparse on the skeletal effects of combination therapy, antiandrogen (bicalutamide) monotherapy has demonstrated an increased BMD from baseline by 2.5% in the lumbar spine at 12 months in men with prostate cancer and no metastases [76]. In addition, this increase in BMD was maintained during monotherapy up to week 96 (2.4% in lumbar spine) [77]. However, in patients with bone metastases, bicalutamide monotherapy is not as effective as an LHRH agonist [78]. Further studies are necessary to determine the optimal use of antiandrogen therapy and its effects on bone health.

## 5. Monitoring of bone mineral density in patients receiving ADT

It has been suggested by an expert panel that men undergoing ADT should have routine assessments of BMD [69]. Dual-energy X-ray absorptiometry of the hip is the preferred method for predicting fractures, and measurement of the posteroanterior lumbar spine is the preferred method for evaluating treatment efficacy [68]. These methods have limitations that must be considered when interpreting results. For example, men 55 years of age or older may develop osteoarthritis in the posterior spine, resulting in an average BMD increase [68].

In addition to the measurement of BMD to evaluate the effects of ADT on the skeleton, other biologic exams such as serum 25-hydroxyvitamin D levels should be considered [68]. A retrospective analysis by Diamond et al. [79] demonstrated that low serum 25-hydroxyvitamin D levels are an important risk factor for spinal fractures during ADT. Supplemental vitamin D intake (400 IU per day) is recommended in this patient population [68].

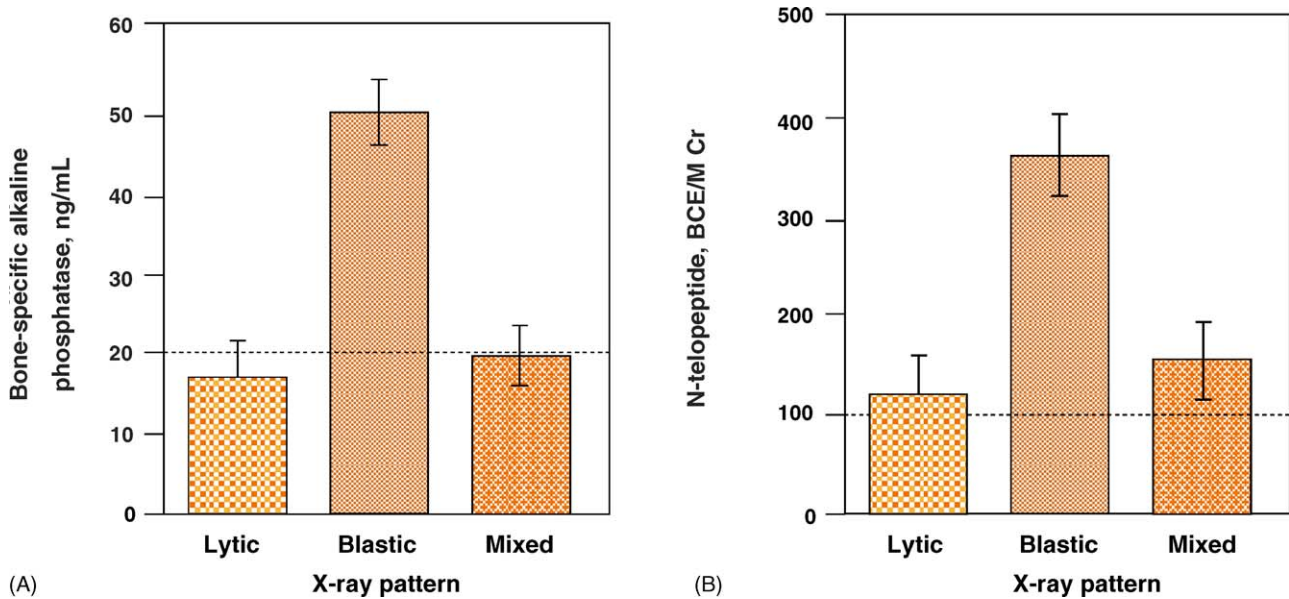
Dietary calcium intake should also be maintained at 1200 to 1500 mg per day. Although dietary calcium intake >2000 mg per day is associated with an increased risk of prostate cancer, there is no indication that the recommended dietary calcium intake is associated with progression of prostate cancer [68].

Biochemical markers of bone metabolism provide insight into the ongoing levels of osteolysis and osteogenesis in patients with malignant bone disease [80]. These markers are generally elevated in patients with metastatic bone disease [55,80,81]. Demers et al. [82] reported that serum BAP and urinary N-telopeptide (Ntx) levels showed a significant correlation with the number of bone lesions and the extent of skeletal involvement in patients with malignant bone disease. In this study, patients with osteoblastic lesions had high levels of both Ntx and BAP, suggesting that they have even higher rates of osteolysis than those with osteolytic bone lesions (Fig. 3) [82]. Additionally, recent evidence has revealed that levels of bone resorption correlate with bone pain intensity and the risk of skeletal complications in patients with prostate cancer [83] and significantly correlate with disease state [84-88], clinical outcome [53,89,90], and likelihood of imminent death [91]. Caution must be used in interpreting levels of bone resorption markers at the time of androgen manipulation, however, as these rise steeply after hormone manipulation of men with bone metastases. This is the result of an osteoclast-mediated destruction of the woven bone within metastatic deposits [7].

## 6. Role of bisphosphonates in prostate cancer

Zoledronic acid, clodronate, pamidronate, and ibandronate have all been investigated in patients with bone metastases from prostate cancer [56,92-95], and all have shown some benefit in terms of pain palliation. However, only zoledronic acid has demonstrated long-term, objective benefits compared with placebo. In a phase III randomized, placebo-controlled trial, zoledronic acid significantly reduced the percentage of patients with skeletal complications and reduced bone pain [56].

Recent studies have demonstrated that IV bisphosphonate therapy can prevent CTIBL in men receiving ADT for nonmetastatic prostate cancer. Compared with placebo, pamidronate (60 mg via 2-hour infusion every 12 weeks for 48 weeks) significantly reduced bone loss in the hip and spine of men receiving the gonadotropin-releasing hormone agonist leuprolide [96]. However, BMD never



**Fig. 3 – Levels of biochemical markers of bone metabolism in patients with osteolytic, osteoblastic, and mixed bone lesions. (A) Serum bone-specific alkaline phosphatase levels. (B) Urinary levels of N-telopeptide of type I collagen. Note the high level of resorption markers in osteoblastic metastases. BCE: Bone collagen equivalents; Cr: Creatinine. Adapted with permission from Demers et al. [82].**

reached baseline levels in this trial. In contrast, in a year-long, randomized, double-blind, placebo-controlled study in 106 men receiving initial ADT, zoledronic acid (4 mg via 15-min infusion every 3 months for 1 year) prevented CTIBL and, additionally, increased BMD compared with baseline levels at all sites measured [97]. After 1 year of treatment, the mean BMD in the lumbar spine increased by 5.6% in the zoledronic acid group and decreased by 2.2% in the placebo group ( $p < .001$ ). These data suggest that zoledronic acid effectively inhibits CTIBL.

Current treatment algorithms for patients with prostate cancer support the use of zoledronic acid to reduce the incidence of skeletal complications from bone metastases and the use of bisphosphonates to prevent bone loss during ADT [69,98]. By reducing osteolysis in patients with early-stage disease, bisphosphonates may better protect patients from skeletal complications later in the disease course and may prevent bone metastasis. It should be noted, however, that not all skeletal complications in this patient population arise specifically from bone metastases.

## 7. Novel treatments for prostate cancer

Although bisphosphonates have demonstrated clinically significant reductions in the incidence of skeletal complications from bone metastases and palliation of bone pain in patients with metastatic

disease, no available therapy has been shown to improve survival or delay disease progression in patients with advanced prostate cancer. Clearly, novel agents are needed to address these issues. Two therapeutic regimens currently being investigated for the treatment of metastatic prostate cancer are the ETs and radionuclides.

### 7.1. Endothelin receptor antagonists

Endothelin-1 is a small peptide that interacts with a G-protein-coupled receptor,  $ET_A$ , to mediate the processes of tissue differentiation, repair, and growth through a complex intracellular signaling pathway. Recently, ET-1 has been implicated in prostate tumor cell progression through signaling of mitogenesis, inhibition of apoptosis, and modulation of angiogenesis and osteogenesis. Endothelin-1 is produced in the prostate gland, and  $ET_A$  receptor expression is up-regulated in prostate cancer [99]. The  $ET_A$  receptor, therefore, represents a valid target for the treatment of prostate cancer.

Recently, the  $ET_A$  antagonist atrasentan (ABT-627; Abbott Laboratories, Abbott Park, Ill, USA) was shown to dose-dependently suppress markers of bone formation in patients with bone metastases from prostate cancer [14]. Patients ( $N = 288$ ) were treated daily with oral atrasentan (2.5 or 10 mg) or placebo for 52 weeks. Over the course of the study, patients receiving placebo experienced a 99% increase in mean BAP levels, whereas patients

receiving 10 mg atrasentan had no increase in mean BAP values from baseline. Treatment with atrasentan also reduced markers of bone resorption compared with placebo.

Two large, multinational, double-blind, randomized, placebo-controlled trials in 2 different prostate cancer populations are currently ongoing. A third study, M00-211, was stopped in February 2003 because it was decided that the study did not meet the primary endpoint of time-to-disease progression [99]. These trials all compared atrasentan 10 mg with placebo. Initial analysis of the M00-211 study suggests that atrasentan provided statistically significant improvements in pain development, mean change in prostate-specific antigen levels, and mean change of biochemical markers of bone progression. The most frequently reported adverse events included headache (14%), peripheral edema (21%), and rhinitis (19%) [99,100]. These trials, therefore, indicate that the ET<sub>A</sub> antagonist atrasentan provides clinically significant benefits for patients with metastatic prostate cancer. Treatment was generally well tolerated; however, because ET antagonists have vasodilatory and fluid homeostasis effects, the potential for side effects on the cardiovascular system are of clinical interest. Further studies and information are anticipated to determine the extent of this effect with atrasentan.

### 7.2. Radiotherapy and radionuclides

Metastatic prostate cancer is associated with severe, debilitating bone pain that is often refractory to supportive care with analgesics. Current therapies to manage pain include external beam radiation therapy and/or radiopharmaceuticals. Radiation therapy has been shown to reduce tumor size, decrease osteolysis, and decrease cancer burden [101].

External beam radiation is typically delivered locally for bone pain. However, it can be delivered systemically if symptoms are widespread. Adverse events including nausea, headache, weight loss, and hair loss are often reported. Late, chronic side effects such as fatigue may also limit the dose of radiation that can be given [102]. Furthermore, in some patients, pain relief may not occur until 4 weeks after treatment [103], and, in approximately 50% of patients, pain relief lasts for only 6 months or less [104]. In Australia and New Zealand, the Trans-Tasman Radiation Oncology Group is conducting a study called RADAR (Randomised Androgen Deprivation and Radiotherapy), comparing the effects of intermediate-term hormone therapy and radiation with or without zoledronic acid in patients with

prostate cancer [105]. Additional studies are required to determine the optimal conditions for treatment of bone pain via external beam radiation.

Use of radionuclide therapy can directly target bone. Metal-chelated radiopharmaceuticals such as <sup>153</sup>Sm-EDTMP and <sup>117m</sup>Sn-DTPA adsorb to the trabecular surface of the bone, whereas <sup>32</sup>P and <sup>89</sup>Sr are more widely distributed in the bone [106]. These agents decay with variable half-lives and emit either beta- or gamma-energy that induces apoptosis in cancerous cells. Although these agents are generally well tolerated, patients may experience bone marrow suppression and/or toxic side effects [107].

## 8. Conclusions

Maintaining bone health in patients with prostate cancer is an important goal. Reductions in BMD occur in patients receiving ADT; therefore, they have an increased risk for skeletal fractures. It is recommended that men undergoing ADT have routine BMD assessments. Current treatment algorithms support the use of bisphosphonates to prevent bone loss during ADT.

Patients with prostate cancer are at high risk for developing bone metastases during disease progression [3]. These malignant bone lesions develop from a complex interplay between metastatic tumor cells and the cellular machinery that repairs and maintains the skeleton [10,48]. Patients with bone metastases from prostate cancer suffer an ongoing risk of skeletal complications, which can contribute considerably to the burden of disease [3]. Retrospective analysis and evidence from the control arms of bisphosphonate clinical trials illustrate the magnitude of skeletal morbidity in patients with advanced prostate cancer and underscore the need for therapeutic intervention [47,53,56,66,92,93].

Zoledronic acid has demonstrated long-term benefits compared with placebo in patients with prostate cancer and bone metastases. Zoledronic acid therapy has significantly reduced the incidence of skeletal complications and bone pain in this patient population. Additionally, recent data suggest that zoledronic acid effectively inhibits CTIBL. The potential benefits of zoledronic acid throughout the natural history of prostate cancer progression continue to be investigated.

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