# *How I Do It: Managing bone health in patients with prostate cancer*

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*Urologists have two scenarios where they have to address bone loss or increased risk of fractures in men with prostate cancer. In the first setting, a patient who has been started on androgen deprivation therapy may develop cancer-treatment-induced bone loss. In the second setting, a patient's prostate cancer may have metastasized to the bone. This article describes six steps to manage bone health in patients diagnosed with prostate cancer in a community practice.*

**Key Words:** prostate cancer, managing bone health

## Introduction

Soon after a man is diagnosed with prostate cancer, he will usually be offered treatment with surgery, radiation, and/or high-intensity focused ultrasound. If the cancer is very advanced or the patient does not want any of these treatments, he is usually offered hormonal therapy (androgen deprivation therapy)—typically a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist, or an anti-androgen. These agents prevent the production of testosterone and its subsequent absorption in the prostate, thereby slowing or preventing prostate cancer growth and spread for a while.

Urologists need to be aware of the potential impact on bone in a patient who is being treated with hormonal therapy, even those who do not have metastatic bone disease. Patients who receive androgen deprivation therapy are at increased risk of fracture,[1] weight gain, and metabolic syndrome. In addition, patients who have high grade or bulky prostate cancer are at higher risk of developing bone metastases and skeletal fractures.[2,3]

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TABLE 1. **Risk factors for bone loss in men**

| | **Risk factors** |
|---|---|
| History and physical examination | Age > 65<br>Recent discovery of loss of height<br>Family history osteoporosis and fractures<br>Vertebral changes on x-ray<br>Bone mineral density test showing osteopenia |
| Lifestyle, nutrition, body weight | Smoking<br>Alcohol > 4 units daily<br>Caffeine > 4 cups per day<br>Lack of exercise: (especially weight-bearing)<br>Lack of calcium<br>Vitamin D deficiency<br>Obesity<br>Weight less than 57 kg |
| Medical conditions | Breast cancer<br>Prostate cancer<br>Malabsorption syndrome<br>Chronic renal disease<br>Hyperthyroidism<br>Chronic obstructive lung disease<br>Hyperparathyroidism<br>Rheumatoid arthritis<br>Hypogonadism |
| Iatrogenic factors | Steroids > 3 months<br>Heparin<br>Anticonvulsants<br>Androgen deprivation therapy |

Consequently, urologists have two scenarios where they have to address bone loss or increased risk of fractures in men with prostate cancer. In the first setting, a patient who has been started on androgen deprivation therapy (medical castration) or a patient who has had surgical castration may develop cancer-treatment-induced bone loss. In the second setting, a patient's prostate cancer may have metastasized to the bone.

With early prescription of calcium and vitamin D supplements and bone targeting treatments, and the ability to monitor bone changes easily and noninvasively, the urologist can manage a patient's bone disease without referring the patient to an oncologist.

Cancer-treatment-induced bone loss manifests as osteoporosis. Risk factors for osteoporosis should be identified in the history and workup of men with prostate cancer, Table 1.

In normal bone metabolism, there is a balance between osteoblasts and osteoclasts and between bone formation and resorption. If this balance is lost, then generalized bone demineralization or osteoblastic or osteolytic lesions are seen on diagnostic images. It is important to perform a bone density test on patients with prostate cancer. This will help identify bone demineralization, degree of osteoporosis, and risk of developing complications such as fractures.

## Method and technique

### Step 1. Diagnose prostate cancer and perform a bone mineral density test

When a patient is diagnosed with prostate cancer, it is important to identify comorbidities and other risk factors for the development of osteoporosis. Men with certain comorbidities, as listed in Table 1, may be at increased risk of developing osteoporosis and cancer-treatment-induced bone loss. Men who have a high risk of osteoporosis should have a bone density test,

a bone scan, or a computed tomography (CT) scan. Certain results on a bone scan suggest that patients are at higher risk for developing osteoporosis.

A bone mineral density T-score of -4 to -2.5 indicates osteoporosis, and a T-score of -1 to -2.5 indicates osteopenia. Patients with osteoporosis, or with osteopenia and either a previous fragility fracture or steroid therapy lasting longer than 3 months or clinical hypergonadism should be treated for cancer-treatment-induced bone loss.

## Step 2. Determine serum calcium, phosphate, and vitamin D levels

Urologists need to determine serum calcium, phosphate, and Vitamin D levels in men who are newly diagnosed with prostate cancer and are candidates for androgen deprivation therapy. These men should be given calcium and vitamin D supplements, as needed. In addition, men with prostate cancer and osteopenia or osteoporosis should also be given these supplements.

## Step 3. Prescribe calcium and vitamin D supplements

The British Columbia Cancer Association and the Osteoporosis Society of Canada recommend that men up to age 70 should ingest 1000 mg of calcium and 600 international units (IU) of vitamin D daily, and men aged 71 and older should ingest 1200 mg of calcium and 800 IU of vitamin D daily. The Canadian Urological Association (CUA) recommends that all men who have been medically or surgically castrated, regardless of age, should ingest 1000 mg calcium and 1000 IU Vitamin D daily.

## Step 4. Diagnose bone metastasis

Bone metastases are usually discovered after a man develops castrate-resistant prostate cancer. In a study of men with advanced, castrate-resistant prostate cancer, 30% presented with visceral metastases, 60% presented with nodal metastases, and 90% presented with bone metastases.[4]

Bone is not only one of the earliest sites of metastasis in castrate-resistant prostate cancer, bone metastases also signal possible skeletal-related events with significant pain and morbidity and increased mortality.

It is important for the urologist to try to detect bone metastases early, because treating these bone lesions can delay cancer progression and reduce skeletal-related events.[5,6] Skeletal-related events or morbidity from bone metastasis could delay, diminish or eliminate the response to future treatments. If bone-targeting treatment is started before metastases are discovered, bone-metastasis-free survival may increase.[7]

Radionuclide bone scans are the most common way to diagnose bone metastases. CT scans are also commonly used. However, in Canada, magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning are not generally used to diagnose bone metastasis.

The longer that a patient has been diagnosed with prostate cancer, the greater their risk of bone morbidity. The risk increases as the patient moves from the hormone-sensitive phase of prostate cancer into and beyond the castrate-resistant phase of metastatic prostate cancer.

In most cases, urologists will look for increasing serum prostate-specific antigen (PSA) levels in patients undergoing hormonal ablation, whether this is medically or surgically induced. A PSA doubling time of less than 8 months is very significant and harbors a very poor prognosis for the patient. The urologist must be diligent in monitoring PSA levels even if a patient appears to have stable PSA levels. If a patient has a rise in PSA levels, it is critical to determine if the patient still has castration levels of testosterone. If the patient is on total androgen blockade, then the recommendation is to stop the androgen, which may sometimes generate a secondary PSA response.

No studies have yet demonstrated that doing random bone scans without evidence of castration resistance will pick up significant numbers of patients with silent bone metastases. It has been shown in bone metastasis studies that patients with or without pain do very well if treatment is delivered early in the disease process.

The urologist must determine if the patient has true bone metastasis. Men who have a steady castration level of testosterone and progression of disease—either with soft tissue or bone metastasis—in association with a rising PSA are castration resistant.

## Step 5. Treat bone metastasis

Although most bone metastases in prostate cancer are osteoblastic, the most successful approach to prevent skeletal-related events may be by using two osteoclast-targeting agents (bone targeting treatments): zoledronic acid (Zometa, Novartis) and denosumab (Xgeva, Amgen).[3]

Urologists need to treat metastatic bone disease to prevent skeletal-related events such as pain that

requires radiation to the bone, pathologic fractures, spinal cord compression, and even bone surgery due to significant bone loss and/or fractures associated with demineralization of the bone.[8]

Early detection and treatment is key. In one study, Saad and colleagues demonstrated that once patients had developed pathological fractures, they had a 23% to 30% increased risk of mortality. Therefore it is important to try to prevent skeletal-related events.[9]

In another study, Smith and colleagues showed that compared with having a baseline PSA below 7.7 ng/mL, having a baseline PSA of 7.7 ng/mL or higher—or, even more conservatively, of 10 ng/mL or higher—increased the risk of death and/or earlier development of a metastasis. In patients with high baseline PSA levels, the authors recommend not waiting until the patient has a short PSA doubling time, but to look for and, if needed, treat metastatic disease.[10]

Before being indicated for the treatment of bone metastasis, zoledronic acid and denosumab had been shown to increase bone mineral density in cancer-free men and women with osteoporosis.

Zoledronic acid is a bisphosphonate that has been shown to inhibit osteoclast activity. It causes impairment in bone resorption by attaching to hydroxyapatite on the bone. It was studied in early clinical trials for men with bone metastasis secondary to prostate cancer.

Denosumab is a synthetic RANK ligand (RANKL) neutralizing monoclonal antibody that prevents osteoclast activity.

There are two main studies of zoledronic acid[5] and of denosumab versus zoledronic acid.[6] In both studies, the active agents were superior to placebo in delaying the time to the first skeletal-related event.

In the study that compared the two agents—denosumab (120 mg given subcutaneously every 4 weeks) versus zoledronic acid (4 mg given intravenously every 4 weeks)—the median time to the first skeletal-related event was 17 months with zoledronic acid versus 20.7 months with denosumab.[6]

Since denosumab is given subcutaneously once a month, it may be more convenient than zoledronic acid, which is given intravenously once a month. In the comparison study, 18% of patients taking zoledronic acid had infusion-site reactions.[6] There is also a high risk of renal failure associated with zoledronic acid, so clinicians must monitor the patient's renal function on a monthly basis to ensure that it is safe to administer the agent.

Prior to prescribing a bone-targeting agent, the urologist must identify a patient's risk factors for osteonecrosis of the jaw (see Step 6).

Once a patient has been prescribed one of these agents, the urologist must monitor a patient's serum calcium levels. After the first 2 months of taking denosumab, a patient is not likely to have significant future fluctuations in calcium levels; variability in calcium levels is higher with zoledronic acid.

Patients with a creatinine clearance below 30 mL/min or on dialysis have a higher risk of hypocalcemia with either bone-targeting agent. These patients must first attain normal serum calcium levels, and they often require a lower dose of zoledronic acid or denosumab.

## Step 6: Monitor patients for osteonecrosis of the jaw

Osteonecrosis of the jaw is a potential devastating side effect of treatment with zoledronic acid or denosumab. Urologists must identify a patient's risk factors for osteonecrosis of the jaw prior to prescribing any bone-targeting agent. Risk factors include dental surgery (the most common cause, 60% to 77% of cases), poorly fitting dentures, poor oral health, a history of oral disease, older age, renal dialysis, smoking, and drugs such as cyclophosphamides, erythropoietin, steroids, and antiangiogenics. Longer duration and increased dosing and frequency of bone-targeted therapy also increase the risk of this complication. Patients receiving bone-targeted therapy require ongoing, regular monitoring of their oral cavities to identify the early development of osteonecrosis of the jaw.

## Conclusion

## Preventing cancer-treatment induced bone loss

Men with prostate cancer who begin taking a castrate-causing agent are at greater risk of cancer treatment-induced bone loss or osteoporosis.

They require baseline calcium and vitamin D assessments, bone mineral density studies, and bone scans. All men on hormonal ablation therapy should start taking and continue to take calcium and vitamin D supplements to bring their calcium and vitamin D levels within the normal range and to help maintain good bone health. They should be aware that smoking and caffeine intake (more than 4 cups a day) can also increase the risk of cancer treatment-induced bone loss. Increased exercise has been demonstrated to reduce the risk of osteoporosis in this setting. Patients must be frequently monitored for osteonecrosis of the jaw, a risk that increases with longterm exposure to androgen deprivation therapy.

## Treating bone health when prostate cancer has metastasized to the bone

Men who have castration resistance, shown by increasing PSA levels, require a bone scan and/ or a CT scan. If the scan shows that a patient has metastatic bone disease, then bone-targeting agents should be prescribed. The patient should have blood tests to determine their baseline serum calcium and vitamin D levels, and they should also have a bone mineral density test. The patient should be prescribed calcium and vitamin D supplements, as needed, to attain normal levels.

A thorough oral cavity assessment should be performed prior to initiating bone-targeting therapy to identify factors that increase the risk of developing osteonecrosis of the jaw.

Once all risks have been mitigated, the patient may be deemed an appropriate candidate for a bone-targeting therapy.

Both denosumab and zoledronic acid have been shown to delay and sometimes prevent skeletal-related events secondary to bone metastases in castrate-resistant prostate cancer. Zoledronic acid may be less convenient, since it is given intravenously. A study reported that 18% of patients receiving zoledronic acid had infusion-site reactions, and there is a need to monitor a patient's renal function every month.[6] With denosumab, as long as the patient's baseline creatinine clearance is above 30 mL/min, there is no need to monitor renal function or be concerned about the onset of renal failure.

With any bone-targeting therapy, it is important to monitor the patient's calcium levels and look for potential development of osteonecrosis of the jaw. □

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