Risk Factors for the Development of Bone Metastases in Prostate Cancer

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Abstract

Objectives: Bone health of men with prostate cancer is threatened throughout the disease course. The majority of patients with advanced prostate cancer will develop bone metastases that can undermine skeletal integrity and result in skeletal complications including pathologic fractures, spinal cord compression, and palliative radiotherapy to bone. The early identification of patients who are at a high risk for bone metastases may enable earlier identification and treatment of bone lesions, thereby preserving patients' independence throughout the disease course.

Methods: Current guidelines for bone health maintenance were reviewed and PubMed key word searches performed to identify risk factors for the development of bone metastases in patients with prostate cancer. Additionally, guidelines and consensus recommendations were reviewed to identify bone health issues and their management in patients with early prostate cancer.

Results: Current prostate cancer monitoring guidelines recommend bone scans at initial diagnosis for patients with prostate-specific antigen (PSA) levels >20 ng/ml and in patients with chronic bone pain or fractures. Multiple studies have concluded that high baseline PSA levels, rising PSA despite androgen-deprivation therapy (ADT), and high PSA velocity are risk factors for the development of bone metastasis in patients with prostate cancer. In patients with early prostate cancer, bone loss is an emerging concern, and bisphosphonates have been demonstrated to prevent bone loss from ADT. Use of risk factors such as PSA kinetics may optimize screening and enable earlier identification of bone metastases.

Conclusions: Monitoring bone mineral density may allow for better preservation of skeletal health in patients undergoing ADT.

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1. **Risk factors for the development of bone metastases in prostate cancer**

Although therapeutic advances have extended overall survival for patients with prostate cancer, maintaining bone health may be challenging throughout the course of the disease [1]. Patients with prostate cancer are at high risk for bone loss induced by cancer treatments, such as androgen-deprivation therapy (ADT), and skeletal-related events (SREs) from bone metastases including pathologic fracture, spinal cord compression, surgery and palliative radiation to bone, and hypercalcaemia of malignancy [2,3]. Therefore, maintaining bone health in patients with prostate cancer requires a multidisciplinary approach to provide optimal clinical benefits to patients throughout the course of their disease [4].

Prostate cancer metastasizes to bone in the majority of patients with hormone-refractory disease [5]. Prostate cancer cells often secrete factors that activate adjacent bone-forming osteoblasts to produce aberrant bone matrix [6]. The resulting osteoblastic bone lesions destabilize the structural integrity of the bone [7]. Osteoclast-mediated osteolysis increases in response to the osteoblastic lesions and can result in decreased bone integrity [6]. This is the underlying cause for most SREs. Moreover, unbalanced osteolysis and osteogenesis during ADT can result in a net decrease in bone mineral density (BMD), placing patients at increased risk for fractures and potentially leaving bone unprotected from invading tumor cells [8,9].

The routine use of bone scans during initial staging of patients diagnosed with prostate cancer remains controversial. Current prostate diagnosis and treatment guidelines from the European Association of Urology (EAU), National Comprehensive Cancer Network, and the European Society for Medical Oncology recommend that radionuclide bone scans be performed at initial staging if patients have prostate-specific antigen (PSA) levels >20 ng/ml, chronic bone pain, or fractures [10–12]. Two independent retrospective analyses, one in Europe and one in China, identified baseline PSA > 20 ng/ml and alkaline phosphatase (ALP) >90 U/l as significant risk factors for the presence of bone metastases at diagnosis [13,14]. A retrospective analysis was performed of 406 patients with prostate cancer who had received a staging bone scan irrespective of their PSA serum level and histology [13]. Results from this study indicated that bone scans were positive in 41 (10%) patients and that EAU guidelines supporting the use of bone scans in patients whose PSA levels are >20 ng/ml were useful with respect to clinical value [13]. Similar conclusions were reached in a retrospective analysis of 96 patients with prostate cancer (29 of whom had bone metastases) and baseline assessments of PSA and ALP and a baseline radionuclide bone scan. Median concentrations of serum PSA and ALP were significantly higher in patients with bone metastases ($p < 0.01$) [14]. Moreover, the percentage of patients with bone scan results was higher in patients with PSA > 20 ng/ml or ALP > 90 U/l versus patients with PSA < 20 ng/ml or ALP < 90 U/l [14].

The Early Prostate Cancer program investigated the optimal PSA cut-off level for recommending bone scans after local therapy for prostate cancer [15]. In this retrospective analysis, data were obtained from protocol-specified bone scans and PSA reports of 4061 patients randomized to standard care alone in the Early Prostate Cancer program [15]. The analysis included 5048 bone scans, and similar to current guidelines and results from other retrospective analyses, the incidence of positive bone scans was low in patients with PSA < 5 ng/ml or < 20 ng/ml who were managed by watchful waiting [15]. Investigators from this study also concluded that bone scans are not indicated in and do not provide any prognostic value for patients with prostate cancer who have low PSA levels [15].

The natural history of disease progression in patients with nonmetastatic prostate cancer and rising PSA levels despite ADT is variable. However, specific risk factors for developing bone metastases have been identified. Smith et al [16] conducted a randomized, placebo-controlled clinical trial to evaluate the effectiveness of zoledronic acid on time to first bone metastasis in patients with prostate cancer, no bone metastases, and rising PSA levels despite ADT [16]. Although this trial was terminated before completion of accrual because the event rate was lower than anticipated, the placebo arm of the trial was used to study the natural history of disease in this patient population [16]. Patients had castrate testosterone levels at study entry, documentation of PSA progression, and no radiographic evidence of bone metastases. Bone scans were performed on these patients every 4 mo [16]. At the 2-yr analysis, 33% of patients had developed one or more bone metastasis, and median bone metastasis-free survival was 32 mo. Baseline PSA and PSA velocity were found to be independent predictors of time to first bone metastasis and bone metastasis-free survival. Specifically, in univariate analyses, baseline PSA levels >10 ng/ml (relative risk [RR], 2.96; 95% confidence interval [CI], 1.63–5.38; $p < 0.001$) and high PSA velocity (RR, 1.47 for each
log (ng/ml)/yr increase in PSA velocity; 95% CI, 1.23–1.75; \( p < 0.001 \) were associated with shorter time to first bone metastasis (Fig. 1) [16]. Baseline PSA and PSA velocity remained statistically significant in multivariate analyses (\( p < 0.001 \) for both; Fig. 1) [16]. Furthermore, in univariate and multivariate analyses, baseline PSA > 10 ng/mL and high PSA velocity were significantly associated with shorter bone metastasis-free survival (\( p < 0.001 \) for both; Fig. 2) [16]. In univariate analyses, Gleason scores >7 were also associated with shorter bone metastasis-free survival (RR, 1.62; 95% CI, 0.96–2.75; \( p = 0.07 \); Fig. 2) [16]. Kaplan-Meier estimates of time to bone metastasis or death demonstrated that a PSA of >24 ng/mL and a PSA doubling time of <6.3 mo are also associated with shorter bone metastasis-free survival (Fig. 3) [16].

A second aspect of bone health involves the development of SREs. Once bone metastases have developed, PSA parameters appear to have limited utility in predicting risk of SRE. For example,
approximately 7% of patients with hormone-sensitive prostate cancer (HSPC) and PSA < 2 ng/ml experienced one or more on-study SRE in a trial in patients with one or more bone metastasis secondary to prostate cancer (n = 308) who received intravenous zoledronic acid 4 mg every 4 wk for 15 mo in addition to standard therapy [17]. Although this proportion of patients is lower than that reported for the overall trial population, which included both hormone-refractory and hormone-sensitive patients (23.0%), these results demonstrate that low PSA levels do not mean that patients are not at risk for SREs [17]. However, although the benefits of bisphosphonate therapy have been demonstrated in patients with bone metastases from hormone-refractory prostate cancer (HRPC), prospective data are needed to determine the optimal role of bisphosphonate therapy in patients with bone metastases from HSPC. A phase 3, randomized Cancer and Leukemia Group B (CALGB-90202) trial of zoledronic acid for the prevention of SREs in patients with bone metastases from prostate cancer undergoing ADT is currently underway to address this issue [18].

As previously stated, ADT decreases BMD and increases fracture risk in patients with HSPC (Fig. 4) [8,19]. This bone loss may exacerbate pre-existing osteopenia or osteoporosis, which is prevalent in patients newly diagnosed with prostate cancer. Notably, preclinical evidence demonstrated that androgen-deficient mice developed significantly more bone metastases compared with control mice, suggesting that excess bone resorption caused by ADT may stimulate metastasis of prostate cancer cells to the bone [9]. Zoledronic acid significantly reduced the incidence of bone metastases in both normal and androgen-deficient mice [9]. Although no bisphosphonate has received regulatory approval specifically for this patient population, clinical data indicate that bisphosphonates may prevent BMD loss during ADT, thereby lowering fracture risk (Table 1) [20–23].

### Table 1 – Bisphosphonates may provide benefits to patients with HSPC by preventing BMD loss during ADT

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>BMD versus ADT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Bruder et al [20]</td>
<td>22</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>Smith et al [21]</td>
<td>47</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Casey et al [22]</td>
<td>139</td>
</tr>
<tr>
<td>Smith et al [23]</td>
<td>106</td>
<td>Zoledronic acid (plus ADT) + mean BMD at the lumbar spine, femoral neck, trochanter, and total hip, whereas placebo + mean BMD (p &lt; 0.001 for all)</td>
</tr>
</tbody>
</table>

HSPC: hormone-sensitive prostate cancer; BMD: bone mineral density; ADT: androgen-deprivation therapy.

emphasizing the need for tools that may assist in identifying patients who may be most in need of therapeutic intervention. Prostate-specific antigen levels and PSA velocity in patients with prostate cancer have been identified as important risk factors and may help identify patients who are at high risk for bone metastases. Although HRPC and prostate cancer that has spread to the bone represent an incurable disease state, the concerted efforts of a multidisciplinary team can provide meaningful treatment benefits [7]. Awareness of risk factors for bone metastases and fractures may enable urologists to identify skeletal health issues before they result in potentially disabling morbidity. The use of bone-targeted bisphosphonates for patients who are at high risk for bone metastases and fractures may reduce the incidence of skeletal complications in these men.

Authorship

Dr. Petrylak was responsible for the generation of this article, controlling the content from its inception, and gave final approval of the submitted version. ProEd Communications, Inc provided medical editorial assistance.

Conflicts of interest

Dr. Petrylak has received honoraria from Novartis Pharmaceuticals Corporation for advisory boards.

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