Skeletal Complications in Patients with CRPC

33

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Abstract

Skeletal complications in patients with prostate cancer can result in significant morbidity. There is a relatively high prevalence of bone metastasis and reduction of bone mineral density due to androgen deprivation therapy, and together, these can result in the development of multiple skeletal complications in patients with prostate cancer. The relatively long survival (median, 3–4 years) after bone metastases with multiple skeletal complications makes a significant negative impact on patients' functional status, quality of life, and social resource utilization. To evaluate skeletal complications, the term "skeletal-related events (SREs)" has frequently been used in most randomized trials conducted previously. SREs usually include pathological bone fracture, spinal cord compression, surgery to bone, and radiotherapy to the bone. Recently, symptomatic skeletal events (SSEs), including only symptomatic events, is the recommended term for use in clinical trials. Local therapies for skeletal complications, such as radiation and surgery, are usually performed to reduce local symptoms, such as bone pain or neurological deficits, leading to improvement of the health-related quality of life. Systemic therapies, such as radiopharmaceuticals, bisphosphonates, and monoclonal antibodies against the receptor activator of the nuclear factor-kappa B ligand, are administered to reduce presymptomatic and symptomatic skeletal complications.

Keywords

Skeletal-related events · Symptomatic skeletal events · Bone mineral density Pathological bone fracture · Spinal cord compression

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33.1 Introduction

Skeletal complications can lead to significant morbidity in patients with prostate cancer by two viewpoints: first, the prevalence of bone metastasis in patients with prostate cancer is relatively higher than that in other cancers [1]; second, androgen deprivation therapy (ADT) for the treatment of prostate cancer reduces bone mineral density (BMD), leading to an acceleration of osteoporosis and bone metastases [2, 3]. These two factors closely interact with each other, leading to the development of multiple skeletal complications in patients with prostate cancer. The relatively long survival (median, 3–4 years) after bone metastases with multiple skeletal complications in patients with prostate cancer makes a significant negative impact on patients' functional status, quality of life, and social resource utilization [4].

33.2 Skeletal-Related Events and Symptomatic Skeletal Events

To assess the incidence of skeletal complications as endpoints of clinical trials, the term "skeletal-related events (SREs)" was previously defined by the Food and Drug Administration of the United States and has been used in several trials [5]. In most clinical studies, SREs included four factors: pathological bone fracture, spinal cord compression, surgery to bone, and radiotherapy to the bone; thus, SREs have been defined as a composite endpoint, mostly including the need for local treatments of radiation or orthopedic surgery ([6–9]; Table 33.1). Radiotherapy is usually indicated for the treatment of uncontrolled pain, pathologic fractures, and spinal cord compression. Surgery usually includes procedures to stabilize or prevent pathologic fractures or spinal cord compression. The definition of SRE, however, is different in several randomized trials. In a broad sense, SREs include a change of antineoplastic therapy to treat bone pain [6, 9]. A reduction in the frequency of SREs has been used in several phase III trials to support the approval of zoledronic acid (ZOL) and denosumab [6, 7]. The definition of SREs includes asymptomatic nonclinical fractures ascertained by serial imaging. Recently, the Prostate Cancer Clinical Trial Working Group 3 [10] stated that they did not consider SREs and instead they recommended using "symptomatic skeletal events (SSEs)" that include only symptomatic events of clear clinical significance. In phase III clinical trial for radium-223, SSEs were defined as symptomatic fracture, radiation or surgery to bone, or spinal cord compression [11].

33.3 Incidence and Prevalence of Skeletal Complications in Patients with CRPC

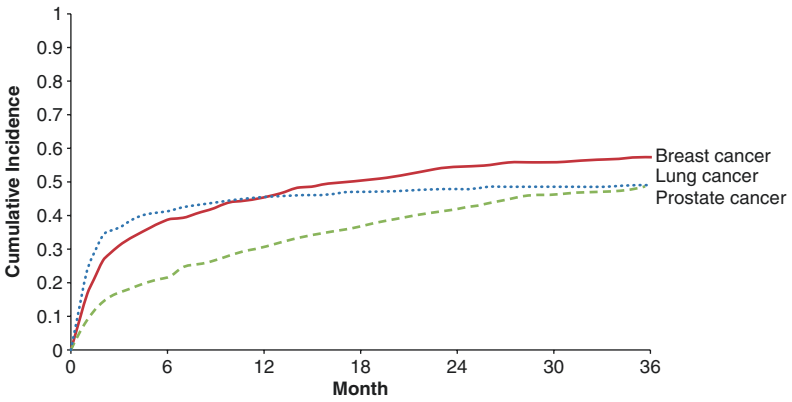
According to data in the placebo arm of the randomized phase III trials evaluating the effectiveness of ZOL, the incidence of SREs was reported to be 44.2% in patients with castration-resistant prostate cancer (CRPC) during approximately 9 months

Table 33.1 Definitions of skeletal-related events (SREs) and symptomatic skeletal events (SSEs) in selected randomized clinical trials conducted in patients with metastatic castration-resistant prostate cancer

Drug	References	Endopoints	Definition of skeletal complications					
			Radiation Therapy	Surgery to bone	Pathological bone fracture	Symptomatic bone fracture	Spinal cord compression	Change of antineoplastic therapy to treat bone pain
Zoledronic acid	J Natl Cancer Inst 94:1458–68 (2002) [6]	Primary: proportion of patients with at least one SRE	○	○	○	–	○	○
		Exploratory: proportion of patients with at least one SSE	○	○	–	○	○	○
Denosumab	Lancet 377:813–22 (2011) [7]	Primary: time to first SRE	○	○	○	–	○	–
		Exploratory: time to first SSE	○	○	–	○	○	–
Abiraterone	Lancet Oncol 13:1210–7 (2012) [8]	Secondary: time to first SRE	○	○	○	–	○	–
Enzalutamide	Lancet Oncol 15: 1147–56 (2014) [9]	Secondary: time to first SRE	○	○	○	–	○	○
Radium-223	Lancet Oncol 15:738–46 (2014) [11]	Secondary: time to first SSE	○	○	–	○	○	–

(median) of observation in the study [6]. Furthermore, all types of pathologic fractures were observed in 22.1%, vertebral fractures in 8.2%, non-vertebral fractures in 15.9%, radiation therapy in 29.3%, bone surgery in 3.4%, and spinal cord compression in 6.7% of patients in the placebo arm. In another study comparing the incidence of SREs in patients with bone metastases in the breast, lung, or prostate cancer, the incidence of SREs in patients with prostate cancer was approximately 20% and 30% at 6 and 12 months after the diagnosis of bone metastasis, respectively, which was less than that in patients with breast and lung cancer. However, the incidence eventually reached approximately 45%, which is comparable to the incidence of lung cancer at 36 months when using ZOL in 48.9% of the prostate cancer patients [12] (Fig. 33.1).

Conversely, the prevalence of bone metastasis and bone pain at the time of CRPC diagnosis was 84% and 45%, respectively, in a Japanese study [13]. In the present study, the medical charts of the enrolled patients with CRPC were retrospectively reviewed at a single institute, and the patients were not using bone-modifying agents, such as ZOL or denosumab. During a median 18 months of follow-up, the incidences of bone pain, neurological deficits, and pathologic fractures were 80%, 44%, and 14%, respectively. The incidences of taking nonsteroidal anti-inflammatory drugs and opioids were 74% and 43%, respectively, and those of radiation therapies for bone pain and laminectomy for paraplegia were 51% and 10% during the follow-up period, respectively (Fig. 33.2).



No. at Risk							
Breast cancer	621	280	186	122	80	57	46
Lung cancer	477	111	46	20	10	7	3
Prostate cancer	721	466	347	257	193	148	118

Fig. 33.1 Cumulative incidence of skeletal-related events (SREs) in patients with breast, lung, and prostate cancers after the diagnosis of bone metastasis

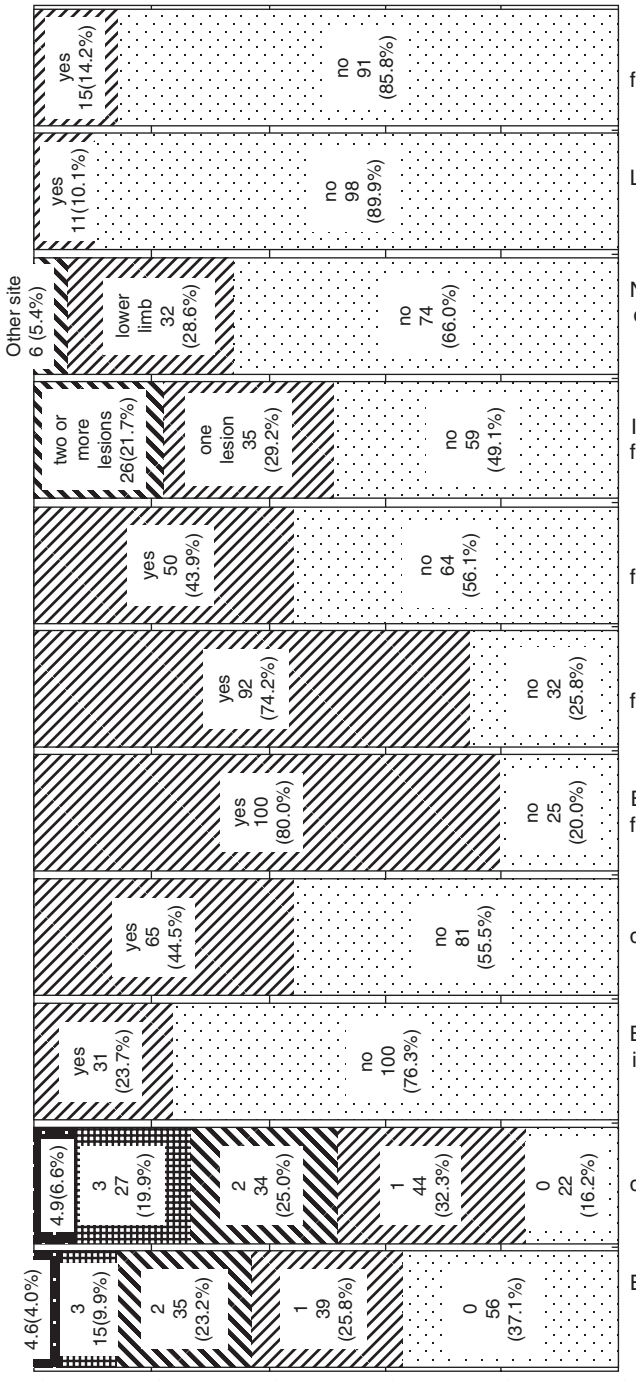


Fig. 33.2 Prevalence of bone metastasis and bone pain at the time of CRPC diagnosis and incidence of skeletal complications during the follow-up period after diagnosis of CRPC

33.4 Pathophysiology of Bone Metastases in Prostate Cancer

The metastasizing mechanism of prostate cancer cells to bone involves colonization of the skeletal microenvironment by circulating tumor cells (CTCs). Reportedly, only 0.2% of experimentally introduced CTCs were estimated to colonize distant sites [14]. According to Paget's well-established "seed and soil" hypothesis published in 1889, a bone microenvironment is ideal "soil" for circulating prostate cancer cells [15]. The three steps of metastatic seeding include survival of CTCs in circulation, homing to skeletal tissue, and attachment to bone parenchyma [16].

Platelets play an important role in the survival of CTCs in that they shield CTCs from NK cell-mediated lysis [17]. In the homing process of CTCs into skeletal tissue, chemotactic factors responsible for the migration of hematopoietic stem cells into bone marrow have been investigated as key molecules [18]. One of these chemotactic factors is stromal-derived factor-1 (SDF-1), also called CXCL12, which is predominantly produced by osteoblasts. C-X-C motif chemokine receptor 4, expressed on the surface of hematopoietic stem cells as well as prostate cancer CTCs, interacts with SDF-1 to induce homing to the bone marrow [19, 20]. In the attachment and invading process of CTCs to bone parenchyma, integrin- and lectin-mediated attachment or protease-dependent invasion has been characterized. Three major integrins, including αvβ3, α2β1, and α4β1, have demonstrated instructive roles in metastatic bone seeding [21].

The activation of osteoclast-mediated bone resorption is one of the most investigated areas in this field. Induction of the receptor activator of nuclear factor-kappa B ligand (RANKL), granulocyte macrophage colony stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF) from the tumor cells results in maturation of osteoclast precursor cells into multinucleated osteoclasts. Enhanced osteoclast-mediated lysis of the bone matrix releases various cytokines, such as GM-CSF, M-CSF, tumor growth factor beta, insulin-like growth factors, epidermal growth factors, fibroblast growth factors, and interleukin 6 stored in the bone matrix. These growth factors stimulate the expression of pro-metastatic factors, such as Jagged 1 [22], parathyroid hormone-related peptide [23], or cathepsin K [24] from tumor cells, which then stimulate the osteoblasts to release RANKL to promote osteoclast activation [25]. These cycles are called "vicious cycles" in the bone microenvironment in that they promote bone metastasis [23, 26].

Prostate cancer typically presents as osteoblastic lesions, and reportedly 43%, 21%, and 36% of the prostate cancer metastases studied in one report were osteoblastic, osteolytic, and mixed, respectively [27]. The transcription factor runt-related transcription factor 2 (RUNX2) is a promising molecule involved in the osteoblastic lesion formation mechanism and is normally expressed by mesenchymal progenitor cells to differentiate osteoblasts. In the microenvironment of prostate cancer bone metastases, RUNX2 is also expressed by prostate cancer cells [28] and activates bone matrix protein transcription, such as bone sialoprotein and osteocalcin. Serin protease Endothelin-1 (ET-1), which is also secreted from prostate cancer cells in the bone microenvironment, is a well-established osteoblast mitogen that promotes osteoblastic bone metastasis by binding ET_A receptor on the osteoblast [29, 30]. The randomized phase III trial for the ET-1 antagonist Atrasentan did not decrease the risk of disease progression in patients with metastatic prostate cancer [31].

33.5 Reduction of BMD Due to ADT and Its Interaction with Bone Metastasis

ADT has been demonstrated to have various adverse effects, including the reduction of BMD. Reportedly, around 45% of patients with prostate cancer receiving ADT develop osteoporosis [32]. The reduction of BMD was maximal in the first year after the initiation of ADT, peaking at 2%–5% [33, 34].

Androgen receptor (AR) is expressed in osteoblasts, osteoclasts, and osteocytes [35–37]. ADT has been shown to increase the levels of RANKL in rat serum and bone marrow [38], which caused a reduction in BMD due to osteoclast activation [39]. Moreover, bone-marrow RANKL mRNA levels have been shown to be up-regulated in mice lacking AR [36, 40] and down-regulated in mice overexpressing AR [37]. Conversely, glucocorticoid promotes the production of RANKL by osteoblasts [41, 42]. Previous reports have suggested that AR regulates RANK/RANKL signaling in the bone microenvironment and that ADT enhances this pathway, inducing osteoclast precursors to mature into osteoclasts, leading to a reduced BMD.

The high prevalence of bone metastases in patients with prostate cancer and reduction of BMD due to ADT together make skeletal complications in these patients more common. In a murine model, Ottewell et al. showed that ADT triggered the growth of disseminated PC3 cells to form bone metastases and that this was prevented with ZOL [2]. Takayama et al. also illustrated the ADT-induced acceleration of bone metastases and involvement of the RANK/RANKL signaling in this interaction [3]. These findings suggest that osteoclast suppression by RANK/RANKL signaling from the initiation of ADT is required to prevent the accelerated establishment of new bone metastases in patients with organ-confined or locally advanced high-risk prostate cancer with a high possibility of the existence of CRPC CTCs at the time of ADT initiation.

In the contemporary oncological strategy for patients with CRPC, relatively long-term ADT (median, 3–4 years) after bone metastasis is usually required. The interactions among the high incidence of bone metastases, reduction of BMD due to ADT, and acceleration of bone metastases due to ADT may together lead to frequent skeletal complications resulting in a poorer health-related quality of life (HRQOL) and survival in patients with CRPC despite the anticancer effect of ADT.

33.6 Prognosis, HRQOL, and Health Resource Utilization in Patients with Prostate Cancer Who Have Skeletal Complications

The presence of SREs is significantly associated with a worse survival and poorer HRQOL. Patients who developed a pathologic fracture had a 32% increased risk of death relative to patients without a fracture in an adjusted analysis, with comparable results observed for both vertebral and non-vertebral fractures [43]. Increasing SRE

Table 33.2 Annual costs of skeletal-related events (SREs)

Variable	No.	Mean (95% Confidence Interval), $
Total SRE costs		
All patients	342	12,469 (10,007–14,861)
Patients with 1 SRE	266	8484 (6810–10,177)
Patients with >1 SREs	76	26,384 (17,959–34,809)
Costs of SREs		
By component		
Therapeutic radiology	342	5930 (4829–7032)
Pathologic fracture	342	3179 (1745–4614)
Bone surgery	342	2218 (1059–3378)
Spinal cord compression	342	460 (116–803)
Other	342	681 (316–1047)
Inpatient vs. outpatient		
Inpatient	342	5641 (3738–7543)
Outpatient	342	5951 (4849–7052)

intensity shows a pattern of poorer survival and HRQOL [44, 45]. In patients with SREs, a significantly worse outcome was observed compared with those without SREs in validated assessment instruments, such as the functional assessment of cancer therapy-general and the brief pain inventory [44]. Complications of osteoporosis and fractures in men undergoing ADT have important economic consequences: there is an associated $22,000 cost per person during the 36 months of treatment [46]. All SREs are associated with health resource utilization, including both inpatient hospitalizations and outpatient or emergency room visits, of $12,469 per year per person [47, 48] (Table 33.2). Furthermore, those studies may have underestimated their impact because of the exclusion of patients with a short life expectancy and health resource with bone pain management [49].

33.7 Treatments for Skeletal Complications

Treatments for skeletal complications include local and systemic therapies. Local therapies include radiation and surgical therapies that are usually performed to reduce local symptoms and improve HRQOL regarding bone pain or neurological deficits. Radiation therapy for local lesions reportedly improves mobility, daily life activity, and sphincter control in patients with metastatic spinal cord compression [50]. Moreover, in one study, radiation therapy significantly improved HRQOL of patients suffering from bone pain [45]. It was reported that functional outcomes after radiation therapy were significantly influenced by the amount of time taken to develop motor deficits before radiation therapy and the number of involved vertebrae. Local control was significantly better after long-course radiation, such as 2 Gy × 20 times, than after short courses, such as 8 Gy × 1 time or 4 Gy × 5 times [51].

Surgical treatments for neurological deficits due to spinal cord compression usually consist of posterior decompression and stabilization with pedicle screws or with pedicle screws and hooks. There have only been a few studies that specifically addressed the surgical treatment of metastatic spinal cord compression in patients with prostate cancer [52–54]. Furthermore, the criteria for which patient may benefit from the surgical therapy of spinal cord compression are poorly defined; in selected patients, however, aggressive surgical decompression and spinal reconstruction is a useful treatment option [54]. Patients with hormone-naive disease and those with the hormone-refractory disease with good performance status and lacking visceral metastases may benefit from surgery for metastatic spinal cord compression [52].

Systemic therapies, including bisphosphonates, a monoclonal antibody against RANKL, and radiopharmaceuticals, are administered to prevent and reduce presymptomatic and symptomatic SREs. The first agent approved for the management of bone metastases in patients with CRPC was ZOL, a third-generation bisphosphonate. A phase III trial comparing ZOL vs. placebo demonstrated a significant reduction of at least one SRE with ZOL from 49% to 38% during the 24-month study period [6]. Denosumab is a fully humanized monoclonal antibody against RANKL that prevents the activation of its receptor RANK leading to inhibition of osteoclast maturation and bone resorption. In a phase III trial comparing denosumab vs. ZOL in patients with CRPC who have bone metastases, there was a significant improvement in median time (3.6 months) to the first SRE in the denosumab arm [7].

Regarding radiopharmaceuticals, strontium-89 is a pure beta-emitter with a long half-life, whereas samarium-153 is a gamma-emitter with a shorter half-life. Multiple randomized trials have been conducted with strontium-89 and samarium-153 in men with metastatic CRPC that have shown no improvement in OS, but palliative benefits have been demonstrated with both agents [55, 56]. The alpha-emitter radium-223 causes breaks in double-stranded DNA with less irradiation of healthy adjacent bone marrow and normal tissues. In a randomized phase III trial, radium-223 significantly prolonged the median OS in 3.8 months and significantly delayed the time to all SRE components, particularly the components of external-beam radiation therapy and spinal cord compression [11].

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