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REVIEW ARTICLE

# Therapy for bone metastasis from different cancers*

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## Abstract

The bone is the most common target organ of cancer metastasis. Bone metastasis leads to considerable morbidity due to skeletal-related events (SREs). These include bone pain, hypercalcemia, pathologic fractures, and compression of the spinal cord. Cancers such as those of the lung, breast, prostate, and kidney are more likely to cause SREs than other cancer types. Additionally, some blood cancers, including multiple myeloma and lymphoma, frequently cause SREs. In this article, we review the conventional therapies for metastatic bone disease, including drug therapy, radiotherapy, and surgery. Among osteoclast-targeting agents, bisphosphonates and nuclear factor kappa-B ligand inhibitors are the most widely used agents to prevent cancer-related bone loss. Unsealed radioisotopes are also considered promising in cancer therapy. Currently, iodine-131, strontium-89, and radium-223 are available for the treatment of bone metastasis. However, the treatments for blood cancers with SREs are different from those of other cancers. In those cases, new classes of agents including proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and histone deacetylase inhibitors have shown remarkable efficacy. We also discuss the potential development of new therapies for these diseases.

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**Key words:** bone metastasis; skeletal-related events (SREs); therapy

Tumor metastasis involves multiple processes, including invasion, embolization, survival in the circulation, arrest in a distant capillary bed, extravasation, and regrowth in the microenvironment of the secondary organ [1]. Metastatic tumor cells must complete all of these processes in order to metastasize. The majority of bone metastases occur in regions with high blood flow, such as the red marrow in the vertebrae, ribs and hips of the axial skeleton. However, they can also occur in other parts of the body, such as the skull, mandible, or femoral head [2–4]. Spinal lesions are predominantly osteolytic, with the new bone forming in response to the destruction of the original bone [2]. The chief presenting symptom of bone metastasis is pain. It is often localized, invariably progressive, and worse at night, due to periosteal stretching and inflammation. In spinal metastasis, radicular pain, numbness, and limited mobility are caused by compression of the spinal cord [5–6]. Furthermore, a fraction of patients with bone metastasis are asymptomatic and the bone metastasis is discovered accidentally during routine bone scans. Timely diagnosis and proper treatment may decrease morbidity, improve quality-of-life (QoL), and, in some cases, even improve survival [7]. In the diagnosis of bone metastasis, single-photon emission computed tomography and fluorodeoxyglucose positron emission tomography (FDG-PET) are particularly valuable as they can identify the precise anatomic locations of the metastases. Magnetic resonance imaging (MRI) and/or computed tomography (CT) should be used to confirm suspected skeletal metastasis. Finally, a biopsy under CT fluoroscopic guidance is crucial for the staging of skeletal metastasis and formulation of the surgical treatment plan [8–9].

In recent years, several new treatment options have become available for patients with metastatic bone disease. Bone modifying agents, such as bisphosphonates and human nuclear factor kappa-B ligand (RANKL) antibodies, are considered the standard of care for reduction of skeletal-related events (SREs) in patients with metastatic bone diseases [10]. In this article, we provide an overview of the conventional therapies and discuss recommendations for the current guidelines regarding the treatment of metastatic bone disease in different cancers.

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## Lung cancer

Lung cancer is one of the most common cancers, and accounts for approximately 20% of cancer-related mortality. Despite advances in anti-cancer therapies such as chemotherapy, radiotherapy and targeted therapies, the 5-year survival rate remains poor (< 15%) [11]. Approximately 40% of patients with lung cancer develop bone metastasis; 22%–59% of those patients experience SREs, which include bone pain, hypercalcemia, pathologic fractures, and compression of the spinal cord. Importantly, these SREs result in QoL deterioration and economic burden [12].

Bone metastasis can be detected in patients with lung cancer patients by measuring carcinoembryonic antigen (CEA) and osteopontin (OPN) levels. Increased CEA and OPN levels may be considered early warning signs, and patients with increased levels need accurate imaging as they are at higher risk of bone metastasis [13]. Fludeoxyglucose (F-18) FDG-PET/CT is the most effective method for the detection of extrapulmonary metastases in lung cancer. Savas *et al* reported that muscular metastasis is not a rare condition; it is frequently detected on F-18 FDG-PET/CT examinations, and often associated with additional distant metastases [14].

The treatment for metastatic bone disease includes drug therapy, radiotherapy, and surgery. Antiresorptive drugs, such as denosumab, and bisphosphonates are recommended for the prevention of SREs in patients with lung cancer and related bone metastases [15]. Denosumab is a bone-targeting agent for the treatment of metastatic bone disease. Zoledronic acid, the most effective bisphosphonate, has been historically considered the standard of care for the prevention of skeletal complications in patients with bone metastasis from lung cancer [12]. The use of unsealed radioisotopes is also considered a promising cancer treatment; it is more target-specific than external beam irradiation and, therefore, may become a more commonly used treatment. Iodine-131 ($^{131}$I), strontium-89 ($^{89}$Sr), and radium-223 ($^{223}$Ra) are currently available for the treatment of bone metastasis. Additionally, a combination of other treatments such as high precision radiotherapy, bisphosphonates, hormonal agents, and molecular targeted agents may also be useful in the treatment of bone metastasis from lung, or other, cancers [16]. Surgery is indicated for bone metastasis from lung cancer when spinal instability, neurologic deficits, and/or intractable pain occur. Instrumented stabilization can decrease pain, improve neurological status, and improve QoL [17–18]. However, arthrodesis may be complicated by associated osteopenia, reduced pulmonary reserve, and a stringent local biologic environment [19].

Finally, systemic therapies including chemotherapy, bisphosphonates, and radioisotopes have shown potential benefit in the management of spinal metastases in certain situations.

## Breast cancer

A recent cohort study reported that the skeleton was the first site of metastasis in 41% of patients with breast cancer. A retrospective study conducted by Rhu *et al* indicated that surgery was beneficial to patients who had metastasis to just a single organ (HR = 0.43, $P < 0.01$); this was particularly true for bone-only metastasis (HR = 0.37, $P = 0.02$) [20]. According to the National Comprehensive Cancer Network (NCCN) guidelines, treatments that target osteoclast activity are of value in patients with metastatic breast cancer in the bone as they can prevent SREs. The bisphosphonates zoledronic acid and pamidronate, and denosumab (a fully human monoclonal antibody directed against RANKL) have been used for this purpose [21–23]. Data from clinical trials have supported the effects of zoledronic acid, pamidronate, and ibandronate in the treatment of breast cancer bone metastasis [24–25]. Local-regional therapies for bone metastasis include palliative radiotherapy (RT) and surgery. RT is used to prevent SREs and to palliate pain [26]. The RT-induced tumor shrinkage leads to reduced mechanical compression and infiltration of the bone tissue. Surgical or RT treatments are usually recommended for patients with symptomatic spinal metastasis [27]; the surgical decompression procedure is effective and neurological function is maintained or improved [28]. Surgery plus RT has been shown to result in a greater effect than either treatment alone [29–30].

According to NCCN guidelines, endocrine therapy or cytotoxic chemotherapy should be adopted as a systematic treatment in patients with bone metastasis, based on tumor hormone receptor and HER2 status. Other suggested treatment agents include the anthracyclines – doxorubicin, epirubicin, and pegylated liposomal doxorubicin; the taxanes – paclitaxel and docetaxel; the anti-metabolite capecitabine; and the non-taxane microtubule inhibitor eribulin.

Additional treatments that target osteoclast activity also play an important role in the treatment of bone metastases. Among osteoclast-targeting agents, bisphosphonates and RANKL inhibitors have been most widely used to prevent cancer-related bone loss [31]. The outcomes of 2 large randomized control trials indicated that treatment with zoledronic acid or denosumab lead to increased bone mineral density and decreased risk of fractures [32–33]. Recently, a collaborative review study indicated that bisphosphonate use resulted in a highly significant reduction in recurrence [relative risk (RR) 0.86, 95% confidence interval (CI) 0.78–0.94; 2p = 0.002], distant recurrence (RR 0.82, 95% CI 0.74–0.92; 2p = 0.0003), bone recurrence (RR 0.72, 95% CI 0.60–0.86; 2p = 0.0002), and

breast cancer mortality (RR 0.82, 95% CI 0.73–0.93; 2p = 0.002) in postmenopausal women, while it had no apparent effect on any outcome in premenopausal women [34]. Intriguingly, Yuen *et al* showed that N-containing bisphosphonates directly bind to the kinase domain of HER1/2 and cause a global reduction in downstream signaling. Lung, breast, and colon cancer cells that are driven by activating mutations or overexpression of HER1 were killed in this way [35]. Pamidronate showed a similar effect on breast cancer cells in *in vitro* experiments conducted by Ponce-Cusi *et al* [36]. Other agents reported to treat painful bone metastases include radiopharmaceuticals ($^{89}$Sr, $^{223}$Ra-dichloride, and samarium-153) [37–39], Cathepsin K inhibitors [40], Endothelin-1 receptor inhibitors [41], and mTOR inhibitors [42].

To evaluate bone metastases, conventional imaging methods such as radiography, diagnostic CT, and MRI are widely used. In addition, biochemical markers of bone resorption (serum C-terminal telopeptide and urinary N-terminal telopeptide, among others) have been proposed for the diagnosis, prognosis, and monitoring of bone metastases [43].

## Prostate cancer

Prostate cancer is frequently associated with metastatic bone disease. More than 90% of patients with castration-resistant prostate cancer (CRPC) have bone metastases [44]. Bone metastases are a major cause of death, disability, and decreased QoL; they also result in increased treatment costs.

Zoledronic acid is the only bisphosphonate that has been shown to reduce both pain and SRE number in patients with CRPC with bone metastases compared with a placebo [45–46]. An association between denosumab, a monoclonal antibody against RANKL, and a reduction in SREs has been reported. However, there was no impact on overall survival in these studies [45, 47].

$^{223}$Ra is a radiopharmaceutical that acts as a calcium mimic. It targets new bone growth in and around bone metastases [48]. It may take only a single particle to kill a cancer cell, and the short penetration results in highly localized tumor cell killing, with minimal damage to the surrounding healthy cells.

External beam radiotherapy is an effective option for pain relief in patients with painful bone metastases. It has been shown to significantly improve symptoms in up to 80% of patients and to completely control pain in approximately 33% of patients [49]. Patients with multiple painful osteoplastic metastases that cannot be conveniently and safely treated by external beam radiotherapy are candidates for radionuclide treatment.

In patients who are expected to live for at least another 2–3 months, surgery for vertebral metastases may be the best treatment option, especially if surgery is likely to result in a functional improvement [50]. The goal is to relieve pain and improve function for the maximum amount of time. It has been shown that stabilization of long bone fractures is almost always justified, unless the patient has reached a terminal stage and death is imminent [50].

Currently, there is a lack of information regarding the use of any specific therapy sequence in CRPC. Therefore, physicians should adhere to the inclusion criteria of the various clinical trials when treating real-world patients with CRPC.

## Kidney cancer

Metastases from renal cell carcinoma are commonly found in the lungs, bone, liver, and brain. To date, these metastases have been mainly treated by drugs such as interleukin-2, gemcitabine, capecitabine, floxuridine, and 5-fluorouracil. In recent years, molecular targeted therapies such as sorafenib, sunitinib, temsirolimus, and bevacizumab plus interferon-α have been used as first-line treatments in metastatic kidney cancer. In particular, the bisphosphonate zoledronic acid is now licensed for use in advanced renal cell carcinoma; it appears to yield a greater benefit in terms of reduction in SREs in bone metastases from renal cell carcinoma than in those arising from other tumor types [51].

Currently, the main local treatment options for bone metastases from renal cell carcinoma are radiotherapy and surgery. A report from Zelefsky *et al* compared single-dose image-guided radiotherapy (IGRT) with hypofractionated IGRT in patients with bone metastases in various locations [52]. The overall actuarial local progression-free survival at 3 years was 44% for all lesions. The 3-year local progression-free survival rates in patients who received a high single-dose (24 Gy; $n$ = 45), a low single-dose (< 24 Gy; $n$ = 14), or a hypofractionation regimen ($n$ = 46) were 88%, 21%, and 17%, respectively ($P$ < 0.001).

Fuchs *et al* reported that patients who had a surgical procedure had better survival rates than patients who had no surgical treatment or a simple biopsy of the local lesion ($P$ = 0.007), with 1-, 3-, and 5-year survival rates of 91%, 60%, and 36% versus 73%, 27%, and 8%, respectively [53]. However, there was no survival advantage for patients who had a wide resection of the lesion compared with patients who underwent an intralesional resection or an intramedullary stabilization alone. They concluded that overall survival rates were higher in patients who had a better preoperative status, metachronous lesions, and in those who underwent a nephrectomy. A wide resection resulted in decreased local recurrences and revision surgeries.

A number of studies have focused on the aspect of pain relief. With a focus on the C1 to sacrum spinal region,

Hunter *et al* studied the efficacy and durability of pain relief achieved with external beam radiotherapy and high-dose stereotactic body radiotherapy [54]. In patients with bone metastases to the spinal column (C1 to sacrum), those authors found that there were no significant differences between pain objective responses ($P = 0.67$), time to pain relief ($P = 0.29$), or duration of pain relief ($P = 0.095$) associated with the 2 treatments.

In summary，surgical resection is a possible treatment for bone metastases from kidney cancer, but the location and accessibility of the metastases, as well as the patient's performance and comorbidities, have to be taken into account. Sometimes，radiotherapy modalities can provide valid, noninvasive, local treatment alternatives to surgery. We recommend the individual evaluation of each patient with osseous renal cell carcinoma metastases prior to treatment.

## Thyroid cancer

Thyroid cancer accounts for only 1% of all new malignant disease. Bone metastasis occurs in approximately 2%–13% of patients with a thyroid malignancy [2, 55–56]. Differentiated thyroid cancer (DTC) accounts for the majority (90%) of thyroid cancer cases, while undifferentiated carcinomas and medullary carcinomas account for < 5% and 5%–10% of cases, respectively. DTC can be further subclassified into papillary carcinoma (70%–75% of cases) and follicular carcinoma (15%–20% of cases) [57]. With the exception of undifferentiated carcinomas, the survival rate in thyroid carcinoma is generally good. The 10-year survival rate in DTC is 80%–95%. However, this rate drops to 13%–21% in DTC patients with bone metastasis [2, 58]. Although follicular carcinoma only constitutes 15%–20% of thyroid cancers, it accounts for the majority of bone metastasis cases [59].

Treatment options for patients with bone metastasis from thyroid carcinoma include radioiodine therapy, pharmacologic therapy, and surgical treatment. There have also been recent advances in radiosurgery and minimally invasive spinal surgery. Surgical resection combined with radioiodine is still the best curative treatment choice, while selective embolization therapy and bisphosphonates are useful modalities in palliation; vascular endothelial growth factor receptor-targeted therapy is particularly useful in non-$^{131}$I-avid disease [60–61].

## Hematologic neoplasms

Bone disease also presents in the majority of patients with hematologic neoplasms, such as multiple myeloma (MM) and lymphoma, and it can seriously affect QoL and survival rate. Bisphosphonates remain the cornerstone of therapeutic management in hematologic neoplasm-associated bone disease. They offer considerable benefit in the prevention or delay of SRE development and in pain relief. Zoledronic acid can also confer survival benefits and, based on the available evidence, it is the superior bisphosphonate; however, its side effects have to be monitored [62]. Denosumab has shown comparable results with zoledronic acid in the treatment of myeloma bone disease. A phase III trial compared subcutaneous injection of denosumab (120 mg/month) with intravenous zoledronic acid (4 mg/month) in patients with solid tumors and bone metastases or MM (10% of the total 1776 patients); they reported that denosumab was not inferior to zoledronic acid in delaying the time to the first on-study SRE [63]. An expanding set of drugs, known as proteasome inhibitors, are also currently under investigation. These drugs have shown potential in reducing the negative effects of myeloma cells on bone cells [63–64]. In addition to agents involved in the suppression of osteoclastogenesis, there have also been developments in terms of other potential therapeutic agents; these include novel immunomodulating agents, as well as proteasome, and RANKL, inhibitors [65].

## Conclusions

Despite significant improvements in local and systemic therapies, bone metastases are still resistant to those therapies, resulting in poor prognosis. Strategies for the management of metastatic bone diseases have shifted; these strategies now focus on delaying exacerbation of skeletal pain and aggravation of metastatic bone diseases. Bone-modifying agents, such as bisphosphonates and human RANKL antibodies, are considered the standard of care for reducing SREs in patients with bone metastatic diseases.

In principle, surgery is indicated for patients with fractures, or risk of fracture, in limb-bone metastasis and for patients with onset of acute spinal paralysis in spinal metastasis. Otherwise, conservative therapies take priority. In patients in whom chemotherapy is remarkably effective, surgery is not required. However, in patients with a single metastasis who are expected to have long survival, the treatment options should include both conservative treatments and surgical treatments [66].

Generally, for bone lesions caused by hematologic neoplasms, surgery is not advisable. Bisphosphonates are the mainstay of myeloma bone disease treatment. Oral clodronate and intravenous pamidronate as well as zoledronic acid are currently used, and seem to have comparable results in preventing disease-associated SREs. Denosumab had comparable results with zoledronic acid in a clinical trial, but its utility has not yet been completely proven. New therapeutic agents are needed to prolong the survival of patients with metastatic bone diseases.

### Conflicts of interest

The authors indicated no potential conflicts of interest.

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