Review Article

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Palliative Radiation Therapy: A cornerstone of Management for Bone Metastases

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Abstract

Bone metastases are a common manifestation of advanced cancer, causing pain, pathological fractures, and metastatic spinal cord compression that significantly impair quality of life. Randomized trials demonstrate that single-fraction palliative Radiation Therapy (RT) provides pain relief comparable to multifraction regimens, although retreatment rates are higher with single-fraction treatment. Multifraction RT remains preferable for patients with favorable prognosis, impending pathological fractures, or when durable local control is desired. Radiotherapy is also integral to the management of metastatic spinal cord compression, often combined with surgery in selected patients. Emerging evidence suggests prophylactic RT may reduce skeletal-related events in high-risk lesions, although further validation is needed. Overall, palliative RT remains a cornerstone of bone metastasis management, providing effective symptom relief and preserving function through individualized, evidence-based treatment.

Keywords: Bone Metastases; Palliative Radiotherapy; Pain Management; Metastatic Spinal Cord; Compression. Skeletal-Related Events

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Introduction

Bone metastases represent a major cause of morbidity in advanced cancer and are the most common indication for palliative radiation therapy (RT). Pain, structural compromise, and neurologic complications substantially impair mobility and quality of life. This article summarizes the epidemiology, biological mechanisms, clinical presentation, and imaging of bone metastases, followed by an in-depth discussion of evidence-based RT strategies, including single-fraction (SF) versus multi-fraction (MF) radiation therapy, management of metastatic spinal cord compression (MSCC), hemibody irradiation (HBI), and approaches to impending pathological fractures. As systemic cancer therapies improve, more patients live long enough to develop skeletal involvement. Bone metastases occur in 30–70% of all cancer patients, and particularly in breast and prostate cancer, where up to 75% eventually present with bone lesions [1-5]. These lesions may cause pain, structural instability, neurological deficits, and hypercalcemia, significantly reducing quality of life. Palliative radiation therapy remains a central treatment modality because it is accessible, effective, and capable of providing symptom relief. Over the past decades, multiple clinical trials have evaluated optimal dose-fractionation strategies, culminating in robust guidelines such as the ASTRO evidence-based recommendations for palliative RT [2-8].

Epidemiology and Anatomical Distribution of Bone Metastases

More than 80% of bone metastases involve the axial skeleton, in which the thoracic spine (70%), lumbosacral region (20%), and cervical vertebrae (10%)[3]. This distribution reflects the high vascular density and supportive microenvironment of red bone marrow, consistent with the "seed and soil" hypothesis.

Other frequently affected locations include the proximal femur and humerus, which are clinically important due to their load-bearing function and susceptibility to fracture.

Biology and Mechanisms of Bone Metastasis

Bone metastases arise from the interplay of tumor cells with the bone microenvironment. Tumor-secreted factors - such as parathyroid hormone-releasing peptide (PTHrP), interleukin-6 (IL-6), and receptor activator of nuclear factor-κB ligand (RANKL) - stimulate osteoclast-mediated bone resorption, leading to osteolytic lesions. In some cancers (e.g., prostate), osteoblastic activity predominates. This dysregulated bone remodeling is central to the pathogenesis of bone pain and structural compromise [7]. Both inflammatory mediators and periosteal stretching contribute to causation of pain, explaining why pain may occur even without overt destruction on imaging.

Clinical Presentation

Bone metastases cause a spectrum of symptoms, most prominently pain, structural instability, and neurological compromise. Pain often represents the earliest and most distressing complaint and may begin intermittently before evolving into a persistent and debilitating symptom. Unlike other cancer-related pains, metastatic bone pain is not reliably correlated with tumor size, histology, or anatomical location, which underscores its multifactorial nature. The transition from intermittent to continuous pain reflects progressive periosteal stretching, inflammatory mediator release, and microfractures within the affected bone. Patients frequently describe a combination of background aching discomfort, movement-triggered pain, and episodic breakthrough pain that overwhelms existing analgesic regimens [8-13].

As metastases progress, the structural integrity of bone may be compromised to the extent that pathological fractures occur. Annual fracture rates range between 5% and 20%, making this one of the most feared complications among both patients and clinicians. Importantly, nearly one in ten patients with skeletal metastases ultimately requires surgical intervention, especially when weight-bearing bones such as the femoral neck or subtrochanteric region are involved. The risk of fracture correlates strongly

with cortical involvement. The works of Van der Linden and colleagues established axial cortical involvement greater than 30 mm and circumferential cortical involvement exceeding 50% as critical thresholds predicting high fracture risk. Metastatic spinal cord compression (MSCC) represents another severe manifestation of skeletal metastasis and occurs in approximately 5–10% of all cancer patients. The majority of cases arise due to posterior extension of vertebral body metastases into the epidural space, although lesions originating from posterior elements or lesions directly invading the vertebral foramen may also cause compression. Clinically, MSCC presents with a spectrum of symptoms including localized back pain, radicular neuropathic pain, muscle weakness, gait disturbances, and autonomic dysfunction such as bowel or bladder function impairment. If left untreated, MSCC can rapidly progress to irreversible paraplegia, therefore prompt recognition and intervention are essential for preserving neurologic function [7-11].

Diagnostic Evaluation

The diagnostic assessment of bone metastases requires a careful synthesis of clinical findings and imaging techniques. Conventional radiographs provide an accessible initial view of gross bone destruction but lack sensitivity for early marrow involvement. Computed tomography offers more detailed characterization of cortical erosion, fracture risk, and subtle structural compromise. Magnetic resonance imaging, however, remains the gold-standard modality for evaluating epi- and intradural disease and detecting MSCC, given its superior ability to delineate soft tissue structures, neural elements, and the presence of thecal sac compression [10-12].

Bone scintigraphy and fluorodeoxyglucose PET/CT contribute valuable insight into the overall metastatic burden, particularly in patients presenting with widespread or multifocal pain. These tools allow clinicians to differentiate between isolated symptomatic lesions that may benefit from local ablative therapy and more diffuse disease that may necessitate systemic treatment or palliative irradiation approaches. Ultimately, imaging not only guides treatment selection but also helps identify patients at high risk of complications such as fracture or neurological deterioration.

Radiotherapy for Painful Bone Metastases

Radiation therapy plays a central role in the palliation of bone metastases, offering effective relief for localized pain, improving mobility, and preventing skeletal-related events. The majority of patients experience significant symptomatic improvement following treatment, with response rates ranging from 60% to 80% and complete pain resolution in up to one-third of cases. These benefits, along with the therapy's non-invasive nature and broad availability (particularly in high-income countries), have established palliative radiotherapy as the most widely used intervention for painful skeletal disease. The goals of radiotherapy extend beyond pain control. By reducing tumor burden within the bone and modulating osteoclast activity, RT contributes to the preservation of mobility and daily functioning. Additionally, it mitigates the risk of future complications such as fracture or neurologic impairment, thereby reducing hospitalizations and improving overall quality of life. Treatment planning increasingly emphasizes interdisciplinary collaboration, in which radiation oncologists, medical oncologists, orthopedic surgeons, and palliative care specialists work together to tailor therapeutic strategies to individual patient needs [14-17].

Evidence from Single-Fraction and Multifraction Radiation Therapy Trials

The optimal radiation dose and fractionation schedule for painful bone metastases has been the subject of extensive investigation over several decades. Numerous randomized trials - including the Bone Pain Trial Working Party study, RTOG 97-14, and the Dutch Bone Metastasis Study - have consistently demonstrated that a single fraction of 8 Gy provides pain relief equivalent to longer-course multifraction regimens such as 20 Gy in five fractions, 24 Gy in six

fractions, or 30 Gy in ten fractions. The equivalence in pain palliation between these regimens has been a major advance in the field, offering patients and clinicians flexibility in treatment selection. Despite similar efficacy in acute pain relief, these trials have also revealed important differences in long-term outcomes. Single-fraction radiotherapy is associated with a higher retreatment rate, with approximately one in five patients requiring a second course of RT for the same lesion, compared to fewer than one in ten patients treated with multi-fraction schedules. This finding is particularly relevant for patients with longer life expectancy or those whose symptomatic lesion is located in a structurally vulnerable region [13].

Hemibody Irradiation for Multifocal Pain

For patients experiencing widespread skeletal pain involving multiple sites, hemibody irradiation (HBI) offers an efficient means of achieving symptom control. Developed primarily for individuals with diffuse metastatic disease that cannot be addressed through localized external beam therapy, HBI has demonstrated response rates between 70% and 80%. The International Atomic Energy Agency's randomized trial compared several upper and lower hemibody regimens and reported an impressive overall pain relief rate of 91%, with nearly half of patients achieving complete responses.

The administration of intravenous fluids, antiemetics, corticosteroids, and analgesics has greatly reduced the risk of acute toxicities of associated with HBI. Myelosuppression remains the most significant limitation and necessitates adequate baseline hematologic function. Because of its significant toxicity profile and the availability of modern treatment techniques, hemibody irradiation is now very rarely employed in countries with advanced cancer care systems. When used appropriately, HBI can reduce reliance on opioids, diminish the need for repeated localized RT, and improve overall quality of life for patients with diffuse symptomatic bone metastases [12-15].

Management of Metastatic Spinal Cord Compression

Metastatic spinal cord compression requires urgent evaluation and treatment. Delayed intervention can result in permanent neurologic deficits, severely impacting functional independence and life expectancy. The objectives of therapy are to preserve or restore ambulation, alleviate pain, stabilize spinal structures, and prevent further neurological progression.

The landmark randomized trial by Patchell and colleagues in 2005 fundamentally changed MSCC management. This study demonstrated that patients who underwent direct surgical decompression followed by postoperative radiotherapy were significantly more likely to regain or maintain the ability to walk than those treated with radiotherapy alone. They also maintained mobility for substantially longer durations and required lower doses of corticosteroids and opioids. Despite these compelling results, surgery remains feasible for only a minority of patients, primarily those with a reasonable performance status, limited levels of spinal involvement, and a life expectancy exceeding three months.

For patients who are not surgical candidates, radiotherapy remains a cornerstone of treatment. Studies by *Rades et al.* compared short-course regimens, such as 8 Gy in a single fraction or 20 Gy in five fractions, with longer schedules including 30 Gy in ten fractions or 40 Gy in twenty fractions. Although overall survival and neurological outcomes were similar between regimens, long-course radiotherapy provided superior local control, reducing the risk of in-field recurrence. These findings support tailoring treatment fractionation to prognosis: patients with limited life expectancy may reasonably receive short-course schedules, while those with more favorable prognostic features may benefit from longer-course therapy [15-17].

Impending Pathological Fractures and the Role of Radiation Therapy

Impending fractures represent a critical therapeutic challenge. Progression from cortical thinning to complete fracture can substantially impair mobility

and require major surgical procedures, which are often associated with risks of complications in patients with advanced cancer. The degree of cortical destruction is the principal predictor of fracture risk, and the criteria proposed by Van der Linden is simple, practical and it may be central to clinical decision making. Lesions with axial cortical involvement exceeding 30 mm or circumferential loss greater than 50% are considered highly unstable. The Spine Instability Neoplastic Score (SINS) is another classification system that can guide clinicians in identifying patients with metastatic disease of the spine who may benefit from surgical procedure.

Radiotherapy plays a dual role in managing these lesions. In cases with minimal to moderate cortical compromise, radiation promotes recalcification and can restore structural strength. Koswig and Budach demonstrated that multifraction regimens such as 30 Gy in ten sessions result in more reliable recalcification compared to single-fraction treatment. Thus, multifraction radiotherapy is often preferred for impending fractures, as it reduces the likelihood of structural failure [2,8,14].

However, when extensive cortical destruction is present, radiotherapy alone is insufficient in preventing pathological fracture. In such circumstances, prophylactic orthopedic stabilization is recommended prior to irradiation to prevent catastrophic fracture. Radiotherapy then complements surgery by addressing residual tumor burden, decreasing postoperative pain, and contributing to long-term structural reinforcement.

Prophylactic Radiotherapy and Prevention of Skeletal-Related Events

Emerging research has explored the concept of using radiotherapy prophylactically to prevent skeletal-related events (SREs) in high-risk metastatic lesions before the onset of pain or structural compromise. Recent prospective data have shown remarkably lower rates of SREs among lesions treated preemptively with radiotherapy compared to those observed without intervention. In one study, only a single event occurred among 62 irradiated metastases, whereas 14 events occurred among 49 lesions in the observation arm. These events included pathological fractures, metastatic spinal cord compression, and the need for emergent palliative radiotherapy.

While these findings are compelling and suggest that prophylactic radiotherapy may dramatically reduce morbidity in high-risk lesions, they must be interpreted with caution. Methodological limitations, such as imbalances in baseline performance status, variable imaging approaches, and heterogeneous definitions of high-risk lesion biology, limit the generalizability of the results. Additionally, radiation for pain relief was counted as a skeletal-related event, raising questions about the clinical significance of these endpoints. Although the early data are encouraging, further phase III trials are required before prophylactic radiotherapy can be widely incorporated into standard practice [6,8,13,17].

Conclusions

Palliative radiotherapy remains a cornerstone of management for bone metastases. Evidence strongly supports the use of both SF and MF regimens, with treatment individualized based on prognosis, risk of fracture, anatomical location, and patient goals. Advances in understanding fracture risk, strategic use of surgery, and emerging prophylactic approaches continue to refine clinical practice.

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