Metastatic Osseous Pain Control: Radiation Therapy

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Abstract

Keywords

- palliative
- radiation therapy
- bone metastasis
- interventional radiology

Metastatic disease to the bone is a common manifestation of advanced cancer, and can result in pain, pathologic fractures, hypercalcemia, and overall functional compromise. External beam radiation is a proven, highly efficacious, and noninvasive therapy that can provide symptomatic relief from painful osseous lesions. When deciding upon the best treatment regimen, it is important to consider patient factors such as overall life expectancy, performance status, disease burden, and site of osseous metastatic pain. Determination of best treatment ideally requires multidisciplinary input from radiologists, medical oncologists, surgeons, pain management, and palliative care specialists together with radiation oncologists.

Objectives: Upon completion of this article, the reader will be able to identify the expected outcomes and utility of palliative radiation therapy in both the initial and reirradiation setting, and describe current guidelines for appropriate use of palliative radiation.

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Metastatic disease to the bone is a common manifestation of advanced cancer, and can result in pain, pathologic fractures, and functional compromise resulting in detriment to overall quality of life (QOL). Primary tumors with predilection of metastasizing to the bone include, but are not limited to, breast, lung, prostate, thyroid, kidney, and myelomas. External beam radiation is a proven, noninvasive, and efficacious therapy that provides symptomatic relief and local control for osseous

metastases with minimal toxicity, providing significant decrease in pain in up to 80% of patients after a single course of treatment.¹ Approximately 30 to 50% of all radiation treatments are delivered with palliative intent (palliative radiation therapy [PRT]).² Rates of PRT use range from 22% to 5–10%, during the final year and last 30 days of life, respectively.^{3–5}

Optimal management of painful osseous metastases may include a combination of approaches including surgery; medications including narcotics, ablation, bone-strengthening agents; and/or radiopharmaceuticals in conjunction with radiation. Determination of the ideal treatment approach requires an individualized approach, with multidisciplinary input from radiologists, medical oncologists, surgeons, and pain/palliative care specialists, as well as radiation oncologists. Additionally, cancer patients undergoing palliative radiation often have short overall life expectancy, though there is significant variation depending on performance status, sites of disease, and primary tumor histology. As such, finding the optimal balance between the potential benefits of treatment, risk of toxicity, and overall burden on patient and caregivers is essential.

Technique

The total radiation dose prescribed (measured in Gray [Gy]), and dose per treatment fraction, determines the number of fractions (or treatment visits) required. Fractionation is dictated by the

need to enable repair of radiation effects in the normal tissues that is inevitably exposed when targeting the area of treatment. In general, patients treated with curative intent RT are given high total doses, in multiple low-dose fractions, resulting in up to 8 weeks of daily RT. In contrast, palliative intent RT can achieve desired outcomes with a lower total dose, typically delivered with a higher dose per fraction, resulting in treatment courses ranging from a single day to several weeks.^{1,6,7} PRT is most commonly delivered with photon beams, using a linear accelerator. Patients undergo a radiation planning scan, typically a CT that images the expected area of treatment, in the same position that will be reproduced for treatment. Afterward, the targeted lesion is delineated by the radiation oncologist, and the best radiation beam arrangement is determined with input from the physician, radiation dosimetrist, and/or physicist. Criteria for choosing for the best plan depend on optimal coverage of the target, maximum sparing of the surrounding normal tissue, daily reproducibility, and total time for delivery. Treatment techniques vary in complexity and conformality, from simple two-dimensional (2D) and three-dimensional (3D) radiation (► **Fig. 1**) to intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) (► **Fig. 2**).

When determining total dose, number of treatments (fractions), and technique, the physician is mindful to select the regimen with highest efficacy, lowest anticipated toxicity, and minimal burden on time/travel. It is assumed that shorter courses of RT will likely place less burden on the patient and caregivers, particularly in the setting of a limited life expectancy. Thus, patients with poor performance status and widespread disease are ideal candidates for shorter, simpler regimens, even if they more likely require retreatment at a later time point.^{8,9} Patients with excellent performance status and limited sites of disease, on the other hand, may be better suited for ablative doses of radiation for a more durable response, with consideration of techniques such as highly conformal SBRT. Onset of pain relief occurs within days to weeks.

Fractionation Patterns

Practice patterns vary widely. According to a survey of 962 radiation oncologists, over 100 different palliative RT regimens for painful osseous metastases were reported, ranging from 1 to 20 fractions in total, though 30 Gy in 10 fractions and 20 Gy in 5 fractions were most common.¹⁰ In general, the most commonly prescribed palliative dose regimens for simple 2D and 3D radiation are 8 Gy in 1 fraction, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and 30 Gy in 10 fractions.

Published national guidelines for osseous metastases support use of shorter PRT courses when possible, with single fraction PRT for uncomplicated bone metastases. The definition of “uncomplicated” osseous metastasis is a bone metastasis without impending or preexisting pathologic fracture, or spinal cord/nerve compression.^{11,12} The American Society of Therapeutic Radiation Oncology (ASTRO) advises against the routine use of extended (>10 fractions) fractionation schemes for palliation of osseous metastases, and endorses use of single-fraction regimens

Fig. 1 Three-dimensional palliative radiation. A patient with diffusely metastatic lung cancer and painful vertebral body metastases treated with PRT. At the time of consultation, he complained of severe 8/10 pain in the lower back, radiating down the right leg at times, with minimal response to pain medications. Lumbar spine MRI revealed diffuse osseous metastases throughout the vertebral bodies, with largest lesions at level of L2–L5 and extension toward the right nerve root at L5. The lumbar spine region was treated to 30 Gy in 10 fractions. Kidneys and bowels were contoured and treatment field designed to minimize radiation dose to normal organs. Two different PRT plans were generated (three-field, and anterior-posterior [AP]: posterior-anterior [PA]); the plan with the least dose to normal organs was selected. Patient was seen in follow-up a month later and reported complete resolution of lower back/right leg pain. (a) Axial view of dose distribution. The 100% isodose line (yellow line) depicts region covered by 100% of the total dose (30 Gy). Radiation beams were opposed AP and PA in direction. Kidneys are contoured with purples and yellow color wash; bowels contoured with orange color wash. (b) Coronal view of dose distribution with AP/PA fields. The radiation field extends out on the right to cover disease extension. (c) Three-field plan was generated using radiation beams from three different angles (posterior wedged pair with an AP beam) to determine whether dose to bowels and kidneys could be minimized. The plan did not improve normal tissue sparing, and was not selected.

Fig. 2 Stereotactic body radiation therapy. Patient with oligometastatic bladder cancer to the right sacroiliac region treated with SBRT in 3 fractions to total dose of 27 Gy. Isodose legend on the left depicts percentage of total radiation dose received. As characteristic of SBRT, the 100% isodose line (27 Gy) is highly conformal, with rapid dose falloff and minimal dose to surrounding normal tissues, allowing higher doses of radiation to be delivered to the osseous lesion. He experienced complete pain relief within 2 weeks of treatment completion.

for patients with poor prognosis, and/or transportation difficulties.¹³ The American Academy of Hospice and Palliative Medicine (AAHPM) Choosing Wisely Guidelines take a stronger stance, stating “don’t recommend more than a single fraction of palliative radiation for an uncomplicated bone metastasis.”¹⁴

Barriers to routine use of single-fraction PRT for osseous metastases have been cited, and include concerns over increased retreatment rates/durability of local control, as well as lack of familiarity with its use.^{12,15} Meta-analyses and a systematic review suggest single-fraction treatment is associated with a higher rate of pathologic fractures.^{1,16} It

is currently unclear whether single-fraction PRT is best reserved for patients with limited life expectancy and poor performance status only. Factors such as patient’s overall life expectancy, tumor location, likelihood of side effects, and performance status should be taken into account when deciding upon a treatment schema.

There are multiple studies demonstrating that shorter courses of palliative radiation are as efficacious as longer courses with regard to pain control and symptom management for uncomplicated osseous metastases (► **Table 1**).^{1,17–21} The Dutch Bone Metastasis Study randomized patients to 8 Gy in 1 fraction versus 24 Gy in 6 fractions, and demonstrated equivalent pain control but higher retreatment rates with single fraction versus multiple fractions (36 vs. 11%, respectively), and a shorter time to reirradiation (25 vs. 39 weeks, respectively). It is possible, however, that higher retreatment rates may be partly explained by radiation oncologist’s willingness to deliver a second course of PRT after a single fraction. A recently presented study demonstrated an association between short-course (5 fractions or less) palliative RT and reduced hospital length of stay, as well as increased likelihood of completing treatment, suggesting shortened PRT is an effective and economical treatment option compared with protracted regimens.²²

Advanced Radiation Techniques in the Management of Painful Osseous Metastases

IMRT and SBRT are advanced techniques that may minimize side effects of treatment, or improve local control/durability by enhancing avoidance of normal tissues, and enabling safe delivery of higher radiation doses to the target. In particular, SBRT for uncomplicated osseous metastases to the spine is an active area of exploration. Prospective studies evaluating use of SBRT for spine metastases have demonstrated high rates of pain control and local control. The University of Pittsburgh

Table 1 Prospective randomized trials of painful bone metastases comparing dose/fractionation schemas for painful osseous metastases

Study	Year	No. of pts	Fractionation	Complete pain relief (%)	Overall pain relief (%)	Retx rate (%)	Toxicity ^a (%)
Bone Pain Trial Working Party ²¹	1999	775	8 Gy/1 Fx	57	78	23	30
			20–30 Gy/5–10 Fx	58	78	10	32
Dutch Bone Metastases Study ⁹	1999	1157	8 Gy/1 Fx	37	72	27	2 ^b
			24 Gy/6 Fx	33	69	5	4 ^b
RTOG 97–14 ¹⁷	2005	898	8 Gy/1 Fx	15	65	18	10
			30 Gy/10 Fx	18	66	9	17
TROG 96–05 ³⁶	2005	272	8 Gy/1 Fx	26	53	29	5
			20 Gy/5 Fx	27	61	24	11
Foro et al ¹⁹	2008	160	8 Gy/1 Fx	15	75	28	13
			30 Gy/10 Fx	13	86	2	18

Abbreviations: FX, fracture; Gy, gray; pts, patients; Retx, retreatment; RTOG, Radiation Therapy and Oncology Group; TROG, Trans-Tasman Radiation Oncology Group.

^aAcute toxicity unless noted otherwise.

^bPathologic fracture rate (see Lutz et al¹¹).

series reports 86% long-term pain control at a median 21-month follow-up after spine SBRT;²³ another study reports overall 87% local control rate.²⁴

Currently ongoing studies include Radiation Therapy Oncology Group (RTOG)-0631, a phase II–III trial randomizing patients with uncomplicated osseous spine metastases to 8 Gy in 1 fraction, versus SBRT to dose of 16 or 18 Gy in 1 fraction. Pain relief, durability of pain control, and toxicity are being assessed.²⁵ Results of this trial may impact current recommendations for uncomplicated osseous spine metastases.

Predicting Prognosis

Patients with osseous metastases have a wide range in prognosis. Given that overall life expectancy is a key consideration when determining the appropriate duration/technique of radiation, a reliable estimation of anticipated survival is important.

In one of the largest studies on bone metastases and radiation, 1,157 patients were treated with PRT for painful osseous lesions, and prognostic factors were evaluated.²⁶ Majority of patients had primary diagnosis of breast (39%), prostate (23%), or lung (25%) cancer. At baseline, mean Karnofsky performance status (KPS) was 70 (range, 20–100), and pain score was 6 (range, 2–10). Median survival of all patients was 30 weeks, and 74% of patients died upon study closure at 2.7 years. A prognostic model was constructed based on patient-reported outcomes and physician-based KPS, and subsequently validated in an external dataset, demonstrating that use of the aforementioned two variables has similar efficacy to a more elaborate predictive model incorporating sex, primary tumor, visceral metastases, KPS, and patient-reported general health and valuation of life. Overall, primary breast cancer patients have the longest median survival, ranging from 8.1 to 20.8 months for median KPS of 20 to 60 versus 90 to 100, respectively; and lung cancer patients have the worst median survival, ranging from 2.0 to 4.7 months for KPS of 20 to 60 versus 90 to 100, respectively.²⁶ According to this study, primary cancer histology and KPS are two simple parameters that can be utilized to reliably estimate median survival. Patients with short-life expectancy and uncomplicated bone metastases would be ideal candidates for single-fraction therapy, whereas patients with longer life expectancy can be considered for more durable, protracted, or complex treatment regimens.

Quality of Life after PRT

A joint American Society of Clinical Oncology (ASCO)/AAHPM Guidance Statement defined nine domains of high-quality palliative care, including EOL care/planning, shared decision making, communication, advanced care planning, and symptom assessment/management.²⁷ According to national surveys involving the AAHPM, National Hospice and Palliative Care Organization (NHPC), ASTRO, and ASCO, greater integration of PRT with palliative care is needed, but barriers include insufficient knowledge among specialties, and inability of most hospice programs to pay for RT.^{20,28}

Since PRT rarely extends life expectancy, and primary goal of treatment is symptomatic relief, QOL becomes an important endpoint alongside pain control. While there are data on the efficacy of palliative RT with regard to the management of physical symptoms, there is a need for data on how treatment impacts other patient-reported outcomes and metrics of quality palliative care. It will be helpful for these tenets of care to be integrated into the delivery of PRT and future clinical trials.

There are very few studies incorporating patient-reported outcomes after PRT.

An analysis of the Dutch Bone Metastases trial reported QOL.²⁹ Overall pain response was 74%, and psychosocial QOL improved slightly after treatment. According to another study, use of PRT improved overall QOL near death when administered to patients with good performance status (Eastern Cooperative Oncology Group [ECOG] ≥ 2), but not patients with poor performance status.³⁰ Moving forward, trials incorporating patient-reported outcome measures in conjunction with clinical outcomes are warranted to provide high-quality data to help direct the use of PRT.

Side Effects of Therapy

Overall, PRT is well tolerated with low toxicity. Conventionally fractionated regimens show acute toxicity rates ranging from 5 to 30%, with side effects dependent on the site of treatment. Common side effects include fatigue, possible nausea/vomiting, diarrhea, or cystitis, depending on the site of the irradiated region; most toxicity is mild and self-limited. Pain flare has been noted after PRT to osseous lesions within days of delivery of treatment, with reported incidence rates up to 44%, and higher likelihood with single-fraction regimens versus multiple fractions.³¹ Typical duration of pain flare is 1.5 days, and some studies suggest a short course of dexamethasone is efficacious in preventing pain flare after PRT.³¹ Pathologic fracture is another potential toxicity after PRT, with higher likelihood after high-dose SBRT or single-fraction treatment.^{9,32}

Reirradiation

As life expectancies improve with advancements in systemic therapy, an increasing number of patients may develop recurrent pain at previously irradiated sites. Reirradiation is a viable option for recurrent osseous pain after initial PRT, with approximately 60% likelihood of pain reduction according to a meta-analysis,³³ and generally acceptable toxicity. In many cases, treatment can be delivered in a single fraction. A multicenter, randomized controlled noninferiority trial (NCIC Clinical Trials Group SC.20) assigned 425 patients with painful, previously treated osseous metastases to 8 Gy $\times$ 1 fraction, versus 20 Gy in 5 fractions,³⁴ and demonstrated single-fraction treatment to be noninferior to multiple fractions. Overall, 45 and 51% of patients treated with single and multiple fractions, respectively, had complete or partial response to reirradiation according to per-protocol analysis. The overall rate of pathologic fracture was 7 and 5% in single-fraction versus multiple-fraction PRT, respectively ($p = 0.15$). A secondary analysis was performed, to determine whether reirradiation resulted in

overall QOL improvement, as measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and Brief Pain Inventory (BPI) at baseline and 2 months postirradiation.³⁵ Results demonstrated significant improvement in overall QOL, and improved functional activity, among the reirradiated responders, supporting the use of reirradiation. Clinically significant improvements in general activity, mood, walking ability, normal work, sleep, and enjoyment of life were noted in responders; nonresponders did not show any significant improvement other than sleep, demonstrating a clear difference between the two groups.

Conclusion

To summarize, radiation is a noninvasive, effective treatment for painful osseous metastases. Benefits include reduction in need for pain medications, local control, and improvement in functional activity that may reflect in QOL. Patients at risk of pathologic fracture may require surgical stabilization prior to radiation. A variety of dose and fractionation regimens exist, with multiple randomized trials demonstrating equivalent pain control and low toxicity among the various schemas. A second course of radiation can be considered for patients who develop recurrent osseous pain after an initial PRT, though overall pain response rates are lower. IMRT and SBRT are more conformal, complex techniques which may be clinically advantageous in select patients, depending on location of metastatic disease, history of prior radiation, and overall disease burden/anticipated life expectancy.

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