

# Radiation for Treatment of Painful Bone Metastases

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## KEYWORDS

- Bone metastases • External beam radiation therapy
- Stereotactic body radiation therapy • Radiopharmaceuticals • Hypofractionation

## KEY POINTS

- External beam radiation therapy (EBRT) effectively relieves symptoms for most individuals with painful bone metastases.
- Hypofractionated EBRT is as effective as a multiple fraction radiotherapy course in most cases, although retreatment rates are higher after a single dose of radiation.
- Stereotactic body radiation is a highly focused form of radiation that may be used in cases of oligometastatic disease, repeat irradiation, and radiation-resistant tumors.
- Radiopharmaceuticals may be used for diffuse bone metastases and have a proven overall survival benefit in patients with castrate-resistant prostate cancer.

## INTRODUCTION

Pain related to bone metastases may be effectively treated with radiation therapy. Patients with bone metastases represent a heterogeneous population in terms of prognosis and extent of disease, some with widespread metastases, and others with oligometastatic disease. Various modalities employ radiation to treat pain, including external beam radiation therapy (EBRT), its offshoot stereotactic body radiation therapy (SBRT), and radiopharmaceutical therapy. Several variables may be considered when deciding on the optimal modality of radiation therapy for each patient, including prognosis, tumor histology, location and extent of metastases, and association with cord compression.

## EXTERNAL BEAM RADIATION THERAPY

External beam radiation therapy (EBRT) is effective at pain improvement in most patients with bone metastases. Various dose and fractionation schedules have been studied and compared, and the optimal approach for every patient may differ.

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Several major prospective clinical trials have evaluated the efficacy of different radiotherapy approaches, including single fraction versus multiple fraction. Overall, the results of the studies suggest that a single fraction of higher-dose radiation may be as effective as a more protracted course of radiation in many patients.<sup>1-6</sup>

### ***Fractionation***

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The first large-scale study to investigate different fractionation schedules was an RTOG study that enrolled patients between 1974 and 1980 and randomized patients with solitary and multiple bone metastases to different regimens.<sup>1</sup> Of the 1016 patients enrolled in the trial, 266 had solitary metastases, and 750 had multiple metastases. Patients with solitary metastases were randomly assigned to treatment with 40.5 Gy in 15 fractions or 20 Gy in 5 fractions. Those with multiple metastases were randomly assigned to 1 of 4 regimens, 30 Gy in 10 fractions, 15 Gy in 5 fractions, 20 Gy in 5 fractions, or 25 Gy in 5 fractions. Response was assessed using a quantitative measure of pain, based on severity and frequency of pain, as well as frequency of pain medication usage. Overall, 54% of patients obtained complete relief, and 89% of patients experienced at least minimal relief. There were no significant differences between any of the treatment arms in terms of degree or duration of pain relief. Of note, patients with higher pain scores prior to treatment were less likely to respond. Also, patients who completed their treatment as planned had a significantly higher rate of complete response than patients who did not complete treatment. Patients with metastatic breast or prostate cancer responded at significantly higher rates than those with lung or other primary cancers. The authors also noted that regardless of the fractionation schedule, pain relief was first noted within the first 4 weeks of treatment, although complete relief was first reported later than 4 weeks in 50% of patients.

In a re-examination of the data at a later date, the biologically effective dose (BED) was calculated for the different treatment regimens.<sup>7</sup> Linear regression analyses of pain response and freedom from retreatment as a function of BED suggested that regimens with a higher BED resulted in improved pain relief and decreased retreatment rates.

In a move from investigating different multiple fraction regimens, the British Bone Pain Trial Working Party conducted a prospective randomized controlled trial comparing a single fraction of 8 Gy with multiple fraction regimens of 20 Gy in 5 fractions or 30 Gy in 10 fractions.<sup>5</sup> Pain relief, as measured by pain severity and analgesic requirements on self-assessment questionnaires, was the primary endpoint. There were no statistically significant differences in the degree of pain relief or in the time to improvement or increase in pain at any time up to 12 months from randomization. The retreatment rate was twice as high after 8 Gy, consistent with other studies.

Dose and fractionation were again investigated in RTOG 9714, in which 898 patients with bone metastases of breast or prostate cancer primaries were randomized to receive EBRT of 8 Gy in 1 fraction versus 30 Gy in 10 fractions.<sup>2</sup> Complete and partial pain response rates at 3 months were equivalent, with pain complete response/partial response rates of 15%/50% for 8 Gy and 18%/48% for 30 Gy. Although patients receiving 30 Gy experienced more acute toxicity (17% vs 10%), those who received 8 Gy had higher retreatment rates (18% vs 9%). This may have been confounded, however, by greater comfort in retreating after 8 Gy on the part of treating physicians. A subsequent subset analysis of patients with painful vertebral bone metastases demonstrated the same results, namely equivalent efficacy with higher acute toxicity for patients receiving 30 Gy (20% vs 10%) and higher retreatment rates for those receiving 8 Gy (15% vs 5%).<sup>3</sup>

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